The clinical and cost effectiveness of hyperbaric oxygen therapy
HTA programme: Systematic Review 2 - July 2008

The clinical and cost effectiveness of hyperbaric oxygen therapy

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1 EXECUTIVE SUMMARY

A review of the range of conditions for which hyperbaric oxygen therapy (HBOT) should be used was commissioned following discussion among the UK Public Health Specialist Commissioner Group regarding National Health Service (NHS) provision of the intervention.

Hyperbaric chambers have been used to treat the effects of decompression illness since the nineteenth century, with HBOT being introduced for the condition in the early twentieth century. HBOT has subsequently been utilised for the treatment of a wide range of medical conditions for which the theoretical basis and/or the evidence of effectiveness is not convincing. The United Kingdom (UK) Department of Health and a number of professional groups have provided guidance on conditions for which they consider HBOT to be appropriate standard care or adjunctive therapy.

This review was based on a horizon scanning report produced by the Agency for Healthcare Research and Quality (AHRQ), USA and attempted to identify all indications for which HBOT has been suggested as an appropriate intervention. Literature searches for reports on the clinical and/or cost effectiveness of HBOT were conducted to identify primary and secondary literature, for the period from 2005 (when the AHRQ report was published) to July 2007. Paediatric studies and reports published in languages other than English were excluded from literature searches. Reports considering the safety of HBOT were included.

A large body of published literature was identified, obtained and critically appraised. The review highlighted a number of practical and methodological challenges when assessing an intervention applicable to such a wide range of conditions. These included: management of the large volume of published reports; appropriate application of evidence hierarchies; appropriate methods for synthesising secondary literature; and making robust recommendations when data are sparse or non-existent.

Randomised controlled trial (RCT) evidence is generally considered to be the gold standard for assessing the efficacy of healthcare interventions. RCT evidence was not available for a substantial number of the HBOT treatment indications. However RCTs may be considered inappropriate for some conditions, such as decompression illness where the theoretical rationale for therapy is accepted. For those conditions where RCTs had been conducted, the quality or reporting of many trials was considered too poor to provide robust conclusions. As a result, therapeutic efficacy was suggested for a number of HBOT indications but rigorous testing is required to confirm the findings. For the majority of conditions considered within this report it is concluded that there is insufficient evidence to support the routine use of HBOT.

For some conditions observational studies have suggested that HBOT may be of some benefit, but conclusive evidence in the form of RCTs is required. A large number of such trials are currently underway and this should provide a better evidence base.

The cost-effectiveness evidence base was limited, with economic evaluations having been carried out for only a few conditions. This review found that most of the cost-effectiveness evidence on HBOT relates to the treatment of diabetic foot ulcers.

A summary of the findings of this review is presented in Table 2.1-1.

Table 2.1-1 Summary of HBOT HTA findings

<table>
<thead>
<tr>
<th>Condition</th>
<th>European consensus conference recommendations(^2)</th>
<th>Report findings</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompression illness</td>
<td>Major accidents should be treated using hyperoxygenation tables at moderate or high pressure. Minor accidents (pain only) should be treated with recompression tables at a maximum of 2.8 atmospheres absolute (ATA).</td>
<td>Empirical evidence together with the theoretical basis and clinical consensus supports the use of HBOT as standard care.</td>
<td>4.2</td>
</tr>
<tr>
<td>Gas embolism</td>
<td>HBOT strongly recommended.</td>
<td>Empirical evidence is lacking, but the theoretical basis and clinical consensus supports the use of HBOT as standard care in severe cases.</td>
<td>4.2</td>
</tr>
<tr>
<td>Carbon monoxide (CO) poisoning</td>
<td>HBOT is strongly recommended for patients with diagnosed CO poisoning, who are at high risk (unconscious; clinical neurological, cardiac, respiratory or psychological symptoms; pregnant women) of immediate or long-term complications.</td>
<td>Empirical evidence together with theoretical basis and clinical consensus supports the use of HBOT as part of algorithms for the management of CO poisoning.</td>
<td>4.3</td>
</tr>
<tr>
<td>Condition</td>
<td>European consensus conference recommendations</td>
<td>Report findings</td>
<td>Section</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Diabetic lower extremity ulcers</td>
<td>HBOT is recommended if peri-lesional trancutaneous oxygen pressures, measured under hyperbaric conditions, are higher than 100 mmHg.</td>
<td>There is some evidence which indicates that HBOT is effective in reducing the number of major amputations required. Ongoing large clinical trials should provide further evidence which may provide support for the routine use of HBOT (see Appendix 7).</td>
<td>4.4.1</td>
</tr>
</tbody>
</table>

Non-diabetic wounds

| Venous ulcers                     | HBOT is recommended if peri-lesional trancutaneous oxygen pressures measured under hyperbaric conditions are higher than 50 mmHg. | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.4.3.1 |

| Pressure ulcers                   |                                                                                                           | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.4.3.2 |

| Other chronic wounds              |                                                                                                           | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.4.3.3 |

| Crush injuries                    | HBOT is strongly recommended in post-traumatic crush injury of Gustilo type III B and C. Measurement of transcutaneous oxygen pressure is recommended to confirm the indication and to direct treatment. | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.4.3.4 |

| Blunt chest injury                |                                                                                                           | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.4.3.5 |

| Calciphylaxis                     |                                                                                                           | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.4.3.6 |

| Grafts and flaps                  | HBOT is recommended for compromised skin grafts and myocutaneous flaps. Measurement of transcutaneous oxygen pressure is recommended to confirm the indication and to direct treatment. | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.4.3.7 |

| Necrotising soft-tissue infections| HBOT is strongly recommended for the treatment of anaerobic or mixed bacterial necrotising soft tissue infection. | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.5.1 |

| Surgical site infections          |                                                                                                           | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.5.2 |

| Livedoid vasculopathy             |                                                                                                           | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.5.3 |

| Acute coronary syndrome           |                                                                                                           | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.6 |

| Stroke                            |                                                                                                           | The evidence does not support the use of HBOT. | 4.7 |

<p>| Traumatic brain injury            |                                                                                                           | There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care. | 4.8 |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>European consensus conference recommendations</th>
<th>Report findings</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft-tissue radionecrosis</td>
<td></td>
<td>There is evidence to support the use of HBOT for patients with radiation-induced proctitis. There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care for patients with other forms of soft-tissue radionecrosis.</td>
<td>4.9</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>HBOT is strongly recommended for radionecrosis of the mandible and recommended for radionecrosis of other bones.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.10</td>
</tr>
<tr>
<td>Cancers and tumour sensitisation to radiotherapy</td>
<td>HBOT is recommended as adjunctive therapy for patients with stage IV neuroblastoma.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care. Ongoing large clinical trials should provide further evidence (see Appendix 7). The adverse events associated with HBOT combined with radiotherapy need to be further evaluated.</td>
<td>4.11</td>
</tr>
<tr>
<td>Orthopaedics</td>
<td>HBOT is recommended for chronic refractory osteomyelitis.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.12</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.13</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.13.1</td>
</tr>
<tr>
<td>Urology</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.14</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>The evidence does not support the use of HBOT.</td>
<td>4.15</td>
</tr>
<tr>
<td>Hearing disorder</td>
<td>HBOT is recommended for sudden deafness but awaits the results of ongoing (2004) RCTs.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.16</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td></td>
<td>The evidence does not support the use of HBOT.</td>
<td>4.17</td>
</tr>
<tr>
<td>Thermal burns</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>There is currently insufficient evidence to support the use of HBOT to treat thermal burns.</td>
<td>4.18</td>
</tr>
<tr>
<td>Sports injuries</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.1</td>
</tr>
<tr>
<td>Condition</td>
<td>European consensus conference recommendations</td>
<td>Report findings</td>
<td>Section</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Osteonecrosis of the mandible</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.2.1</td>
</tr>
<tr>
<td>Peridontitis</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.2.2</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.3</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.4</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.5</td>
</tr>
<tr>
<td>Pain syndromes</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.6</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td></td>
<td>The evidence does not support the use of HBOT.</td>
<td>4.19.7</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>HBOT is optional in acute ophthalmological ischaemia.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.8</td>
</tr>
<tr>
<td>Infertility</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.9</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.10</td>
</tr>
<tr>
<td>Malignant otitis externa</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.11</td>
</tr>
</tbody>
</table>
2 INTRODUCTION

2.1 Purpose of the review

This review originated from discussions of the UK Public Health Specialist Commissioners group, regarding the range of conditions for which hyperbaric oxygen should be used. This review was based on a horizon scanning report published by the AHRQ in the USA1 and attempted to identify all indications for which hyperbaric oxygen has been suggested as appropriate therapy. The commissioners requested that, based on the quality of the evidence, the conditions were classified into one of the following groups:

- of proven benefit and cost effective, so should be used in the NHS
- of proven benefit but not cost effective, so should not be used in the NHS
- of unproven benefit but with sufficient suggestion of possible benefit for trials to be worth doing – use in trials only
- of proven lack of effectiveness – not for use.

It was agreed with the report commissioners that literature searches would not be restricted to RCTs and high quality evidence but would also include lower quality studies, to demonstrate the range of conditions for which HBOT is currently used and the basis for such use. There is also a notable lack of RCT evidence for some of the conditions which may be the result of difficulties in providing appropriate sham treatments; blinding subjects to the pressurisation process; recruiting subjects to regimes which may involve daily attendance for 8 weeks; and difficulty in securing research funding.

Decompression illness was included within this review for completeness, though not included in the AHRQ report as HBOT is considered the standard care for this condition.

2.2 Hyperbaric oxygen as therapy

Hyperbaric chambers have been used since the mid 1600s, with the first reports of recompression to treat decompression sickness among caisson workers appearing in the mid-1800s2. In 1924 the USA Navy first published standardised recompression treatment schedules and, following an animal study on the use of oxygen for the treatment of decompression sickness, oxygen breathing was included in 19393. The clinical use of HBOT to improve the effects of radiotherapy in cancer patients and to reduce the risk of cardiac arrest during heart surgery were reported in 19554. HBOT is an accepted treatment for decompression sickness, arterial gas embolism and severe carbon monoxide (CO) poisoning but has also been used for a wide range of other medical conditions. For many such conditions the theoretical basis for use is unclear and/or the evidence of efficacy is not convincing5. When used to treat decompression illness, therapeutic effects are due to the physical properties of the component gases. Boyle’s law states that the volume of gas is inversely proportional to the pressure exerted on it, assuming no change in temperature. The aim of therapy is to eliminate bubbles from the blood and tissues where they may cause mechanical obstruction. HBOT achieves this in two ways. Firstly the bubbles are compressed according to Boyle’s law, and secondly, the establishment of a low partial pressure of nitrogen in the plasma will encourage diffusion of nitrogen out of the bubble via the plasma to the alveoli where it can be expired6.

It has been hypothesised that the intermittent application of high plasma partial pressures of oxygen during HBOT enables diffusion of oxygen into hypoxic tissues. This then restores immune function, angiogenesis and healing in chronically hypoxic tissues where wounds have failed to heal at normal oxygen levels.

The Department of Health states, in the specialised services definition for hyperbaric oxygen7, that HBOT should be used for the following conditions:

- emergency treatment
  - decompression illness
  - air and gas embolism
- urgent treatment required within 24 hours
  - CO poisoning
  - necrotising faciitis
  - gas gangrene
- elective treatment
  - osteoradionecrosis (ORN)
  - diabetic wounds.

The British Hyperbaric Association has approved the following conditions for treatment with hyperbaric oxygen (http://hyperbaric.org.uk/conditionsTreatment.htm):

- decompression sickness
- gas embolism
- CO and smoke inhalation
- gas gangrene
- selected aerobic and anaerobic soft-tissue infections
- refractory osteomyelitis
- radiation injury
- exceptional blood loss anaemia
- crush injury and other acute traumatic peripheral ischaemias
- skin grafts and flaps
- healing of selected problem wounds
- thermal burns
- intracranial abscess.

The 2004 European consensus conference2 indicated that there is sufficient evidence, in the form of expert consensus opinion, to recommend HBOT for the following additional conditions:

- surgery and implant in irradiated tissue (preventative action)
- sudden deafness
- neuroblastoma stage IV
- post-anoxic encephalopathy
- postvascular procedure reperfusion syndrome
- limb replantation
- pneumatosis cystoides intestinalis.
2.2.1 Hyperbaric chamber facilities and treatment

Hyperbaric chambers can either be monoplace or multiplace chambers. Monoplace chambers are less costly and are portable but multiplace chambers may allow an assistant or nurse to enter to care for the patient or deal with emergencies and are less claustrophobic. Patients inhale pressurised oxygen via a hood or mask in a multiplace chamber. In common with previous literature analyses, no attempt was made in this review to compare the relative effectiveness of mono- versus multiplace chambers.

Hyperbaric chamber pressures do not normally exceed 3 atmospheres absolute (ATA) and standard treatment for decompression illness takes 4–5 hours. For other conditions treatment usually lasts up to 2 hours, although the number of sessions required is highly variable.

2.2.2 Hyperbaric facilities

Within the UK, hyperbaric oxygen facilities are located in a number of institutions including: hospitals, Royal Navy centres, diver training units and private organisations. Hyperbaric chambers are classified into four groups dependent on the availability of medical facilities, suitability for different types of patients and whether they use mono- or multiplace chambers.

2.2.3 Current use of hyperbaric facilities

The British Hyperbaric Association collates information on HBOT treatments carried out in participating-member chambers. For the most recent time period available (January 2005–December 2006), 675 patients were treated, 42% for decompression illness, 32% for radiation-damaged tissue and 7% for CO poisoning. The remainder of patients were treated for a range of conditions, including those not covered by the recommendations of the European consensus conference. When considered in terms of treatment sessions, approximately 63% were for radiation-damaged tissue and 17.5% were for conditions indicated by the Undersea and Hyperbaric Medical Society (UHMS) but not by the European consensus conference.
3. METHODS

3.1 Literature searches

Clinical effectiveness

An initial search to identify evidence such as review articles, health technology assessment (HTA) reports and treatment guidelines was undertaken in July 2007. This was supported by a number of submissions from the topic proposers.

A systematic search for primary and secondary literature was undertaken in July 2007, using the following sources:

- MEDLINE
- EMBASE
- Cochrane Database of Systematic Reviews, Issue 2, 2007
- Cochrane Central Register of Controlled Trials
- HTA database
- Database of Abstracts of Reviews of Effects
- NHS Economic Evaluation Database (NHS EED)
- Health Economics Evaluation Database (HEED)
- The Science Citation Index (SCI).

Restrictions were applied limiting the results to English language articles and literature published from 2005 onwards, as the AHRQ report had systematically searched the evidence prior to this date. The reference list of the AHRQ report was also used to identify source material.

A list of the sources searched and a copy of the search strategies are provided in Appendix 2. These strategies were used to search MEDLINE and this strategy was adapted for use with other databases.

Current awareness alerts were set up to identify papers published after completion of the literature search.

A further literature search was conducted in October 2007 to identify papers on decompression sickness or gas/air embolism. As these conditions were excluded from the AHRQ report, the search retrieved papers published from 1966–2005.

Cost effectiveness

Evidence to assess cost effectiveness was obtained from a variety of sources. NHS EED, HEED and websites of health economics research units were searched for relevant economic evaluations. A copy of the strategy used to search the MEDLINE database is presented in Appendix 2 and this strategy was adapted for use with other databases.

A separate systematic literature search for economic studies was not performed in MEDLINE or EMBASE. Instead the clinical effectiveness data were examined for relevant economic information. In addition, a small number of studies were identified by scanning the bibliographies of retrieved items and as part of the report submission process.

3.2 Inclusion and exclusion criteria

Two researchers independently screened all titles and abstracts to ensure the relevance and consistency of the selected literature. Any discrepancies in the perceived relevance of specific papers were resolved by consensus.

Full text papers, thought to be relevant based on the title and abstract, were obtained where possible. The relevance of each study was assessed according to the inclusion and exclusion criteria outline in Table 3.2-1. Studies which did not fulfill all criteria were excluded with reasons being documented.

Cost effectiveness

For cost-effectiveness analyses, the criteria from Table 3.2-1 were augmented by further inclusion criteria, requiring that studies report both costs and outcomes of HBOT versus one or more alternative treatments.

A flow chart indicating the number of papers found and how these have been used is given in Appendix 3.

### Table 3.2-1 Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any study design</td>
<td>Animal studies</td>
</tr>
<tr>
<td>Any size study</td>
<td></td>
</tr>
<tr>
<td>Systematic reviews</td>
<td>Narrative reviews, meeting abstracts, editorials, letters to the editor and opinion papers</td>
</tr>
<tr>
<td>Full English text</td>
<td>Studies published in languages other than English</td>
</tr>
<tr>
<td>HBOT as mono- or adjunctive therapy</td>
<td></td>
</tr>
<tr>
<td>Adult population</td>
<td>Paediatric studies</td>
</tr>
</tbody>
</table>
Data extraction

The data from the clinical effectiveness studies selected were extracted into tables as presented in Section 4. Studies selected for cost-effectiveness analyses are presented in Section 6. Two independent reviewers considered the data from each article and discrepancies were resolved by consensus.

Quality assessment

The Scottish Intercollegiate Guidelines Network (SIGN) methodology checklists were used to assess the quality of the selected studies, though formal quality scores were not assigned.

If one or more systematic review or HTA were identified, these were to form the main evidence base. Individual trials published since the most recent systematic review were also reviewed. In the absence of systematic reviews and controlled trials, other controlled studies (e.g., cohort and case control studies) were considered. Case series and studies were only considered if no high-level evidence was available and were assessed in the context of a high likelihood of bias.

As this mainly was a review of reviews, there was no attempt to evaluate the potential for bias in interpretation of trial results on the basis of sources of funding or conflict of interest. It has been shown that external funding is associated with publication independently of the statistical significance of results (www.cochrane-handbook.org). The potential for publication bias in favour of more positive outcomes should therefore be considered where commercial interests are involved.
4 RESULTS

4.1 Previous HTA reports

Four HTA reports that assessed the effectiveness of hyperbaric oxygen for a number of indications were identified. These were published by the AHRQ in the USA, Medicare Services Advisory Committee (MSAC) in Australia, the Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé (AETMIS) and the Calgary Regional Health Authority. A systematic review carried out by the West Midlands Development and Evaluation Service, to determine whether there was sufficient evidence to support a business case for a local hyperbaric facility, was also identified.

The AHRQ report was supported by a MEDLINE search of studies published in English from 1966–2005, supplemented by searches of Cochrane, guideline and AHRQ technology assessment databases, and hand searching of the references lists of selected articles and textbooks. The AHRQ authors presented only the reported study findings and made no attempt to assess quality or synthesise the data.

In the MSAC report a comprehensive literature search was carried out supported by: searches of electronic databases, attempts to identify the grey literature, reference list scanning and expert input. This report considered literature published in English from 1966–1999 and assessed all HBOT indications identified by the initial literature search. Independent study review was undertaken and quality assessment was conducted in accordance with the Cochrane Collaboration Handbook. Where possible, outcome data were combined to give pooled efficacy estimates.

The AETMIS report conducted a more limited search of studies published in English and French, identified from the MEDLINE database. These were supplemented by hand searching the bibliographies of identified reports. No indication was given of the methodology used to assess study quality and no pooling of results was undertaken. Narrative summaries were presented.

The West Midlands report involved a search of MEDLINE, Toxline, BIDS, the Cochrane Controlled Clinical Trials Register and citations, and sought expert input. Predetermined inclusion and exclusion criteria were applied to the identified literature, and data from selected references were abstracted by one reviewer. No statement was made as to how the quality of the selected studies was assessed. Narrative summaries of the findings were presented.

Mitton and Hailey reviewed the literature on the effectiveness of HBOT for 13 conditions recommended by the UHMS at the time of publication. The literature search included the MEDLINE, HealthSTAR, CINAHL and EMBASE databases, with citation searching and input from researchers and clinical experts. No statement was made as to the reference selection process or quality assessment procedures used. A narrative summary of the results was presented.

A PhD thesis produced by Bennett also considered a range of indications for HBOT. Much of the work presented in this thesis was published in a series of Cochrane reviews.
4.2 Decompression illness

Introduction

The development of gas bubbles within body tissues is known as decompression sickness, and results from rapid decompression after spending time at raised environmental pressure. Inert gas dissolves in the tissues when an individual is breathing gas at pressures higher than normal. The most common situation where this happens is self-contained underwater breathing apparatus (SCUBA) diving. The development of gas bubbles within the tissues or blood vessels is associated with decompression back to 1 ATA that is too rapid to allow elimination of this excess gas safely through the lungs. This is called decompression sickness or the bends. Bubbles are common in the venous circulation during decompression, but if they enter the arterial circulation through the lungs they may be associated with profound neurological injury. This is called cerebral arterial gas embolism (CAGE) and may be clinically indistinguishable from decompression sickness. These conditions are collectively termed decompression illness. CAGE may also be caused by trauma, including iatrogenically during surgery, and in this case is not associated with decompression at all.

Gas bubbles can cause mechanical blockage of blood and lymphatic vessels giving rise to a number of pathological symptoms including: skin itching, joint pain (bends), fatigue, a build up of venous gas emboli in the pulmonary circulation (chokes), and neurological effects ranging from visual disturbance to quadriplegia.

Both decompression sickness and gas embolism can be treated by recompression and subsequent decompression with slow ascent. Recompression reduces the size of the dissolved gas bubbles, allowing reoxygenation of tissues and minimising inflammatory reactions.

Diving pressure tables have been developed using mathematical models of the ascent process that are dependent on the depth and duration of descent. However, there is biological variability in pressure responses and individuals can undergo physiological adaptation to work at high pressure. The applicability of the various models is, therefore, the subject of ongoing debate and experimentation.

Air recompression was standard procedure for compressed air workers, according to the UK statutory instruments, until 2001. Routine oxygen decompression was approved by the Health and Safety Executive (HSE) in 2001, as a result of their work on respective rates of bubble formation during air and oxygen recompression. Air recompression has been shown to be effective in the treatment of caisson workers with decompression sickness but, possibly as a result of changes in occupational practices, HBOT has become standard treatment for this indication.

Guidelines for the treatment of both altitude decompression sickness and diving-related decompression illness have been agreed by the Aerospace Medical Association and the UHMS. The scientific evidence supporting the use of HBOT is limited to observational studies and a few trials considering the use of drugs as adjunctive therapy to HBOT. The more recent literature pertaining to both conditions is summarised below.

Evidence identified

Two HTA reports considering the use of HBOT for the treatment of decompression sickness and gas embolism were identified. A total of 15 case series reports of decompression sickness were identified by the literature search.

A Cochrane review assessing the effectiveness and safety of recompression and adjunctive therapies for decompression sickness identified two RCTs. These are detailed in Table 4.2-1. Of the case series identified by literature search, 10 reports of decompression sickness studies that recruited more than five subjects are detailed in Appendix 4. Data were not extracted from the remaining reports. Twenty additional case studies were identified and details of these can be provided on request.

Evidence quality

HTA reports were limited in the search strategies used and identified only a small number of studies for inclusion. The case series identified by our searches of the primary literature were of mixed quality, although some were quite large and attempted to identify all cases treated at a particular hyperbaric facility or for a particular condition within a specified time period. Only a few reports made specific reference to the level of missing data within study cohorts.

Case series reports and other observational studies are known to be subject to poor reporting. They do not include a control group and the potential relationship between the intervention and outcome cannot be clearly assessed. All case series reports are subject to selection bias, unless they specifically recruit consecutive patients. In the case reports identified the number and reasons for patient discontinuation from the study were often omitted.

Results

The AHRQ report did not assess decompression sickness and gas embolism, as HBOT was considered standard care for these conditions. The report of the Australian MSAC did not review the literature on use of HBOT to treat decompression illness and air or gas embolism. However, it did recommend that public funding for HBOT be made available, as it represents standard therapy for these conditions and alternative treatment options are limited.

AETMIS and Mitton and Hailey indicated that there is an acceptable level of evidence to support the use of HBOT for treatment of decompression sickness. The AETMIS HTA reviewed the use of HBOT for gas embolism...
and reported that, although the evidence was not robust, the studies identified did indicate that the treatment was effective.

The Cochrane review\textsuperscript{18} reported no differences in the recovery outcomes of patients receiving non-steroidal anti-inflammatory drugs (NSAIDs) or heliox as compared with standard oxygen therapy. There was an indication that these adjunctive therapies reduced the number of recompression sessions required. These findings may be due to the effective analgesic treatment of mild pain, reducing the requirement to re-treat though underlying pathologic processes may still be ongoing. The authors identified a need for large clinical trials considering the use of different breathing gases in recompression therapy.

The remaining case series indicated that a large number of decompression sickness cases are effectively treated by HBOT, with 30–98% of patients achieving full recovery. The lowest proportion of patients experiencing full recovery was reported for a group of Moskito Indian divers, many of whom experienced long delays (>48 hours) between symptom onset and treatment\textsuperscript{24}.

The three case series considering gas embolism provided conflicting evidence on the benefits of rapid HBOT therapy. However comparison between studies was difficult due to the relatively small size, insufficient detail reported on the relative severity of patient symptoms and use of different treatment schedules.

**Discussion**

There were indications\textsuperscript{25,27} that heterogeneity in the diving population (military, commercial and recreational divers) may result in variations in the type of decompression stress experienced and the potential effectiveness of treatments.

The evidence for the use of HBOT as adjunctive treatment to recompression in the treatment of decompression sickness is limited. Changes in recompression regimen regulations advise routine oxygen recompression and as a result HBOT has been adopted as standard treatment for this condition. Furthermore, the cost implications of providing HBOT in addition to recompression are negligible.

Issues relating to the appropriateness of different treatment schedules remain. These relate to the use of breathing gases and the differential treatment responses in different diver groups (military, professional and recreational) which may relate to their physical characteristics, frequency of exposure to diving conditions and time between symptom onset and treatment.

The evidence for the effectiveness of HBOT for gas embolism is less robust. However the theoretical basis for treatment, clinical consensus and data from observational studies have led to HBOT becoming standard treatment for severe cases\textsuperscript{10}.

Further research on optimal treatment schedules is warranted and could be achieved by conducting high-quality studies of registry data, rather than undertaking new RCTs.
Bennett et al., 2007

**Systematic review**

To examine the effectiveness and safety of recompression and adjunctive therapies in the treatment of decompression illness.

Search of CENTRAL, MEDLINE, EMBASE, CINAHL and a specialised hyperbaric database, and hand search of texts, journals and conference proceedings. No language limitations were applied.

All randomised and quasi-randomised trials on decompression illness were included. Patients with other causes of arterial gas embolism were excluded.

2 RCTs were used. In one trial of 180 patients there was no evidence of improved effectiveness on addition of an NSAID (tenoxicam) to recompression therapy (RR 1.04; 95% CI: 0.90, 1.20; p=0.58) though there was a reduction in the number of recompressions required (p=0.01). The second trial of 88 patients indicated that the likelihood of multiple recompressions was lower using a helium/oxygen table compared with oxygen (RR 0.56; 95% CI: 0.31, 1.00; p=0.05).

Recompression therapy is standard treatment for decompression sickness, although there is no supportive RCT evidence. The addition of NSAIDs or heliox may reduce the number of treatment sessions required but does not improve recovery. The authors urged cautious interpretation due to the relatively small size of the trials.

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Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé, 2001

**HTA**

To review the effectiveness of HBOT in the treatment of various conditions.


Studies in English or French.

Included 1 case series of HBOT for treatment of gas embolism following cardiac surgery and 1 RCT comparing HBOT and dexamethazone treatment of mountain sickness. Despite reliance on the theoretical basis for therapy and data from observational studies, HBOT is the standard treatment for both conditions.

---

Mitton & Hailey, 1998

**HTA**

To detail the available evidence on the effectiveness of HBOT, and the possible economic impact on health care of establishing a second HBOT facility in Alberta.


Included studies considered as the highest level of evidence for each indication.

Identified only reviews and level V evidence. Identified one case series of 14 patients treated for arterial gas embolism and the case series of 6 patients treated for gas embolism following cardiac surgery. Given the theoretical evidence, observational study data, widespread clinical use and early work, HBOT is the treatment of choice for decompression sickness. The authors commented on the lack of high-level evidence.

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Table 4.2-1 Evidence on using HBOT to treat decompression sickness - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim(s)</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett et al., 2007</td>
<td>Systematic review</td>
<td>To examine the effectiveness and safety of recompression and adjunctive therapies in the treatment of decompression illness.</td>
<td>Search of CENTRAL, MEDLINE, EMBASE, CINAHL and a specialised hyperbaric database, and hand search of texts, journals and conference proceedings. No language limitations were applied.</td>
<td>All randomised and quasi-randomised trials on decompression illness were included. Patients with other causes of arterial gas embolism were excluded.</td>
<td>2 RCTs were used. In one trial of 180 patients there was no evidence of improved effectiveness on addition of an NSAID (tenoxicam) to recompression therapy (RR 1.04; 95% CI: 0.90, 1.20; p=0.58) though there was a reduction in the number of recompressions required (p=0.01). The second trial of 88 patients indicated that the likelihood of multiple recompressions was lower using a helium/oxygen table compared with oxygen (RR 0.56; 95% CI: 0.31, 1.00; p=0.05).</td>
<td>Recompression therapy is standard treatment for decompression sickness, although there is no supportive RCT evidence. The addition of NSAIDs or heliox may reduce the number of treatment sessions required but does not improve recovery. The authors urged cautious interpretation due to the relatively small size of the trials.</td>
</tr>
<tr>
<td>Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé, 2001</td>
<td>HTA</td>
<td>To review the effectiveness of HBOT in the treatment of various conditions.</td>
<td>Limited electronic database search and bibliography scanning. Covered literature in databases to July 1999.</td>
<td>Studies in English or French.</td>
<td>Included 1 case series of HBOT for treatment of gas embolism following cardiac surgery and 1 RCT comparing HBOT and dexamethazone treatment of mountain sickness.</td>
<td>Despite reliance on the theoretical basis for therapy and data from observational studies, HBOT is the standard treatment for both conditions.</td>
</tr>
<tr>
<td>Mitton &amp; Hailey, 1998</td>
<td>HTA</td>
<td>To detail the available evidence on the effectiveness of HBOT, and the possible economic impact on health care of establishing a second HBOT facility in Alberta.</td>
<td>Literature search of electronic databases, reference list scanning, expert opinion. Searched database to 1997.</td>
<td>Included studies considered as the highest level of evidence for each indication.</td>
<td>Identified only reviews and level V evidence. Identified one case series of 14 patients treated for arterial gas embolism and the case series of 6 patients treated for gas embolism following cardiac surgery.</td>
<td>Given the theoretical evidence, observational study data, widespread clinical use and early work, HBOT is the treatment of choice for decompression sickness. The authors commented on the lack of high-level evidence.</td>
</tr>
</tbody>
</table>

RR = relative risk CI = confidence interval
Table 4.2-2  Evidence on using HBOT to treat gas embolism - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim(s)</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/ exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benson, et al., 2003&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Case series</td>
<td>To review outcomes of patients receiving HBOT to identify prognostic factors for treatment outcome.</td>
<td>Review of case files at Hennepin County Medical Center, USA of patients treated with USA Navy tables 6 or 6A.</td>
<td>All patients diagnosed with iatrogenic cerebral arterial gas embolism from 1987–1999.</td>
<td>19 patients were treated with HBOT. 5 recovered completely, 11 showed improvement, 1 experienced no change and 2 could not be assessed. At 2 months post-therapy, 8 patients had recovered completely, 6 showed partial recovery and 5 patients died. The incidence of recovery was not significantly different for patients with venous versus arterial gas embolism.</td>
<td>The authors noted no difference in recovery when comparing patients with delays to treatment and those treated within 6h. All patients who died had a Glasgow Coma Scale of 3 at the time of treatment. This was a small series study with a high mortality rate.</td>
</tr>
<tr>
<td>Blanc et al., 2002&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Case series</td>
<td>To assess the relationship between treatment delay and clinical outcome.</td>
<td>Review of case files at the department of intensive care and hyperbaric medicine, Marseille, France. HBOT was 6 ATA for 10 min followed by 2 ATA for 60 min with 100% oxygen. Patients not experiencing total recovery had second course 24h later at 2 ATA for 60 min with 100% oxygen.</td>
<td>All patients experiencing air embolism from 1980–1999 treated according to an identical hyperbaric oxygen schedule.</td>
<td>86 patients were treated for iatrogenic cerebral air embolism. Of 84% of patients with venous air embolism, those treated within 6h had better outcome than those with a delay of &gt;6h (p&lt;0.05). Of patients with arterial air embolism, there was no difference in outcome in those experiencing a longer treatment delay (p=0.7). 58% of patients showed good recovery, 35% had sequelae and 7% died.</td>
<td>The authors encouraged early treatment of patients with cerebral air embolism, although they noted that recovery may also be possible following long delays to treatment.</td>
</tr>
<tr>
<td>Leitch &amp; Green, 1986&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Case series</td>
<td>Review of the effectiveness of recompression therapy for uncomplicated pulmonary barotraumas (PBT) and arterial gas embolism (AGE).</td>
<td>Review of diving accident files at Institute of Navel Medicine, Gosport, UK.</td>
<td>Review of all cases of PBT and AGE from 1965–1985.</td>
<td>140 cases of PBT, of which 23 were uncomplicated and 117 experienced AGE. 21% recovered spontaneously. 15 cases of uncomplicated PBT were recompressed. Of AGE patients, around 50% improved spontaneously. Of treated patients a 65% success rate was observed. Of the 31 cases not cured, there was 1 death, 1 deterioration and 14 patients remained unable to walk at the end of treatment.</td>
<td>Authors concluded it was difficult to compare the different treatment schedules.</td>
</tr>
</tbody>
</table>
4.3 Carbon monoxide poisoning

Introduction

CO is the most common cause of fatal poisoning in the USA and Europe\cite{31,32} and HBOT is widely used as a therapeutic intervention. Breathing oxygen under hyperbaric conditions increases the dissolved oxygen concentration in the blood, but does not affect the oxygen bound to haemoglobin. At 3 ATA, the dissolved oxygen level in blood approaches 60 ml/l, which is sufficient for tissues to maintain resting metabolism. CO has higher haemoglobin binding affinity than oxygen and binds to form carboxyhaemoglobin. This results in a reduced arterial blood oxygen concentration. Hyperbaric oxygen at 3 ATA reduces the half life of carboxyhaemoglobin in blood to 15–30 minutes, compared with a half life in air of 4–6 hours. This provides the theoretical basis for the use of HBOT in promoting the supply of oxygen to tissues following CO poisoning\cite{36}.

HBOT is considered standard therapy following significant exposure to CO in many health care systems.

Evidence identified

A Cochrane systematic review of RCTs comparing HBOT with normobaric oxygen (NBOT) for the prevention of neurological sequelae in patients with acute CO poisoning\cite{34,35}. The review identified six RCTs, published from 1989–2004. One RCT was excluded from the Cochrane review because it only reported on a surrogate endpoint; the study is not described here as it does not provide additional useful information. An earlier review, published in 1994, described RCT data available at that time and four observational studies published from 1968–1992 comparing HBOT and NBOT\cite{36}. The use of HBOT for CO poisoning is also considered in the HTA by Mitton and Hailey\cite{11}, which identified evidence from four RCTs and one controlled trial published from 1989–1995. Two of these RCTs are also considered in the Cochrane review\cite{34,35}. Updated searches did not identify subsequent RCTs comparing HBOT with NBOT. The studies informing on the use of HBOT to treat CO poisoning are described in Table 4.3-1.

Evidence quality

The Cochrane review was well conducted\cite{34,35}. Several sources were searched up to October 2004, without language restriction, to identify relevant RCTs. The review applied explicit inclusion criteria and systematically assessed quality. Of the six RCTs included, two double-blind trials achieved the highest quality score (5 of 5), three non-blind trials scored 3 of 5 (blinding was not possible in two trials as control group patients did not enter a hyperbaric chamber) and one scored 2 of 5. However, scoring may give an inflated indication of study quality because it does not take into account allocation concealment or the extent of loss to follow up (which was over 50% in one trial). None of the RCTs reported adequate allocation concealment, which is an important potential source of selection bias. All the trials reported losses to follow up, with reasons. The review authors identified other design flaws in the trials that may have introduced bias.

The observational studies included in the 1994 review were comparative case series with methodological limitations including: bias towards the use of HBOT in more severely affected patients, non-standardised treatment protocols, lack of sham control procedures, incomplete follow up and lack of adjustment for confounding factors\cite{36}.

Mitton and Hailey\cite{11} report only limited methodological details for retrieving and selecting studies, making it difficult to assess the robustness of the findings.

Results

The Cochrane review considered 1,335 participants randomised to HBOT or NBOT\cite{34,35}. One trial was only published as an abstract and for another only interim data were available. The severity of CO poisoning and specific HBOT and control interventions used varied greatly between trials. Only two trials compared HBOT with a sham procedure to enable double blinding.

The primary outcome of interest to the review was the presence of persistent signs or symptoms, indicative of neurologic injury at 4–6 weeks follow up. Outcomes were defined and measured differently in each trial. Meta-analysis of the six RCTs (n=1,335) identified no statistically significant difference in neurologic sequelae (persistent signs or symptoms, as defined in each trial) between HBOT and control interventions. The review authors advised cautious interpretation of the pooled analysis, which may have been inappropriate given the marked clinical and statistical heterogeneity between trials. The findings were not consistent across all six trials; two showed significant benefit for HBOT and four showed no difference from the comparator. It was not possible to establish whether this was due to different patient populations and treatments, or flaws in study design\cite{34,35}.

Mitton and Hailey\cite{11} reported the results from four RCTs, two of which were included in the the Cochrane review, and one controlled trial. The study findings were presented separately and no evidence synthesis was performed. Of the two RCTs not included in the Cochrane review one showed a significant decrease in persistent and delayed neuropsychological sequelae in the HBOT group and the other a non-significant difference between HBOT and control treatment.

The earlier review included four comparative case series (n=515), two of which were retrospective, published from 1968–1992\cite{31}. None of the studies provided reliable estimates of the clinical effectiveness of HBOT relative to NBOT in comparable patient populations.

No adverse event data were reported in these studies.
Discussion

The evidence primarily related to late neurological effects observed with severe CO poisoning. However, the greatest theoretical advantage of hyperbaric oxygen is that it is the fastest and most reliable method of reversing CO poisoning. A rapid recovery time would be expected to be associated with fewer days in hospital, however trials did not report on this outcome.

RCT evidence concerning the clinical effectiveness of HBOT for CO poisoning, compared with NBOT, is conflicting. Concerns over flaws in study design and potential bias cast doubt on the reliability of RCT findings published to date.

The conflicting findings from clinical trials need to be considered in the light of the theoretical basis for HBOT therapy for CO intoxication and current consensus among clinical experts. Guidance has indicated criteria for selecting patients for HBOT versus NBOT, the appropriate treatment schedule to reverse the acute effects of exposure, and the use of additional therapy to limit delayed neurological sequelae. A recent review has proposed that HBOT is clinically indicated for patients if any of the following criteria apply: unconscious at the scene or hospital; new neurologic deficit or mental status change; show end organ ischemia; carboxyhaemoglobin of greater than 25% (or 20% for pregnant women). The British Hyperbaric Association indications for emergency HBOT treatment are: neurological deficit; cognitive impairment; clinical evidence of myocardial involvement; pregnancy; history of sustained loss of consciousness and inability to assess adequately (eg concurrent drug overdose). The evidence available would indicate that it is appropriate to include the use of HBOT in algorithms for the management of carbon monoxide poisoning.
## Table 4.3-1 Evidence on using HBOT to treat CO poisoning – included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim(s)</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juurlink et al., 2005(^{34}), Buckley et al., 2005(^{35})</td>
<td>Cochrane systematic review</td>
<td>To assess the effectiveness of HBOT compared with NBOT to prevent neurologic sequelae in patients with acute CO poisoning.</td>
<td>MEDLINE, EMBASE, CENTRAL, reference lists and expert opinion.</td>
<td>RCTs in adults with acute CO poisoning, comparing HBOT with NBOT. Exclusion criteria: pregnancy, reporting of surrogate outcome data only, and lack of data on neurological sequelae at 1 month. There was no language restriction.</td>
<td>6 RCTs included 1,335 participants. None reported adequate allocation concealment, 2 were double blind. 1 trial had &gt;50% loss to follow up. Interim data only were available for 1 trial. Meta-analysis of all 6 RCTs showed no statistically significant difference in neurologic sequelae between HBOT and NBOT at 4–6 weeks follow up. The trials were clinically heterogeneous and the results inconsistent: 2 trials showed significant benefit for HBOT and 4 showed no difference. Reasons for differences between trials were not established.</td>
<td>RCTs did not establish whether HBOT reduced the incidence of adverse neurological sequelae.</td>
</tr>
<tr>
<td>Mitton &amp; Hailey, 1998(^{11})</td>
<td>HTA</td>
<td>To detail the available evidence on the effectiveness of HBOT, and the possible economic impact on health care of establishing a second HBOT facility in Alberta.</td>
<td>Literature search of electronic databases, reference list scanning and expert opinion. Searched to 1997.</td>
<td>Included studies on CO poisoning considered to be of the highest evidence level.</td>
<td>Identified 4 RCTs and 1 controlled trial. Results were reported separately and were contradictory.</td>
<td>Further evidence is required to establish HBOT as the best treatment for patients with CO poisoning.</td>
</tr>
<tr>
<td>Tibbles &amp; Perrotta, 1994(^{36})</td>
<td>Systematic review</td>
<td>To assess the efficacy of HBOT versus NBOT for CO poisoning.</td>
<td>MEDLINE and the Defense Technical Information Centre, National Technical Information Service and UHMS databases and reference list scanning.</td>
<td>RCTs and prospective non-randomised comparative studies in adults or children comparing HBOT with NBOT were eligible for inclusion. Language restriction was unclear.</td>
<td>2 RCTs including 369 participants and 4 case series (n=515) were included. The observational studies were biased towards the use of HBOT in more severely affected patients and did not adjust for potential confounding.</td>
<td>Mortality and morbidity advantages were not demonstrated in blinded RCTs. Scientifically robust studies are needed to definitively establish the clinical efficacy of HBOT in CO poisoning.</td>
</tr>
</tbody>
</table>
4.4 Wounds

Introduction

Wounds result from numerous different aetiologies but all have areas of oxygen deficient tissue. HBOT is thought to accelerate wound healing and reduce wound infection by increasing the supply of oxygen to damaged tissues. Hyperbaric oxygen greatly increases plasma oxygen partial pressure. By doing this it aids diffusion-dependent oxygenation, driving oxygen further from the capillary. It is suggested that as a result, it aids tissue oxygenation in angiopathic conditions including diabetic ulcers (Dr JA Ross, Senior Lecturer, University of Aberdeen. Personal communication, January 2008). HBOT was considered as an adjunct to standard care for wounds. Given the differing nature of the wounds, however, standard care varies greatly and is continually evolving.

Section 4.4.1 considers diabetic lower extremity ulcers, as the evidence identified for this indication is greater than for all other wound settings. In addition, diabetic lower extremity ulcers have a major impact on health service use; the amputation rate in diabetic patients is estimated at 15–20 times that in the general population. Various other wound types are discussed in Section 4.4.2, including venous and pressure ulcers, other chronic wounds, crush injuries, calciphylaxis, skin grafts and flaps.

4.4.1 Diabetic lower extremity ulcers

Evidence identified

Six HTAs and seven systematic reviews met the evidence inclusion criteria. The methods and results of the Cochrane review were included in the review by Roeckl-Wiedmann et al., and so these two publications were considered together. Two evidence based guidelines were also identified. These guidelines addressed all aspects of diabetic ulcer treatment and only discussed HBOT briefly and so are not considered further in this report. No additional trials to those included within the secondary literature were identified. One retrospective cohort study was included as it was the only study providing data on predictors of HBOT treatment success. A further cohort study from Australia also investigated predictors of success but only the results of an interim analysis were available. One case study was identified but the data were not extracted given the amount of secondary literature available. Studies informing on the use of HBOT to treat diabetic lower extremity ulcers are described in Table 4.4.1.

The HTAs and systematic reviews all sourced a similar small group of primary studies that varied depending on whether they limited inclusion according to study design.

Evidence quality

In general the HTAs and systematic reviews conducted comprehensive searches to identify evidence; reported the inclusion and exclusion criteria used to select studies; combined studies appropriately; and drew conclusions that reflected the evidence. A pragmatic approach to evidence synthesis was adopted in the CADTH study, to provide inputs for an economic model. However, the report failed to consider variations in study design and size.

All HTAs and systematic reviews were limited by the small number of primary studies available and the small numbers of patients included (eg the RCTs identified included 18–70 patients). The primary studies were also of varying quality, with most inadequately reporting methodology and outcomes. Synthesis of the primary study data was complicated by variable entry criteria (in terms of wound severity and duration and extent of complicating infection), differences in treatment regimens and the extent of blinding. The comparator treatment in most studies was ‘standard wound care’, however the precise definition differed between studies. Some studies used placebo HBOT as a comparator.

Results

Many HTAs and systematic reviews summarised the findings of earlier reports. As a result, only the studies of Roeckl-Wiedmann et al., ECRI and MSAC are discussed here. Other studies were consistent with these reports. Roeckl-Wiedmann et al. only considered RCTs and provided the most current and robust evidence base. The ECRI and MSAC reports include the same two RCTs and three controlled trials, two of which were identical and supplemented the Roeckl-Wiedmann et al. data.

Four main patient-centred outcomes were considered in the studies:

- risk of major amputation (above or below the knee)
- risk of minor amputation (of the toe or forefoot)
- the proportion of wounds healed
- reduction in wound size.

Risk of major amputation

Based upon the results of three RCTs, Roeckl-Wiedmann et al. reported the relative risk of major amputation in the HBOT treatment group to be 31% (95% CI: 13%, 71%) lower than that in the control group. MSAC considered two RCTs and three controlled trials and reported a 25% reduction in the likelihood of major amputation in HBOT treated patients (95% CI: 13%, 50%). The results remained significant after sensitivity analysis; although caution must be exercised in interpreting the results of the Roeckl-Wiedmann et al. meta-analysis due to the small number of events.

Risk of minor amputation

Roeckl-Wiedmann et al. and MSAC reported non-significant increases in the relative risk of minor amputation in the HBOT group of 2.2 times (95% CI: 0.58, 8.72; data from two RCTs) and 1.76 times (95% CI: 0.68, 4.59; data from two RCTs and one controlled trial) respectively, compared with the control group. Neither report indicated whether the studies were adequately powered to show a difference in this outcome, however given their small size this seems unlikely.
Risk of amputations

ECRI\(^47\) combined RCT and controlled trial data for major and minor amputations, and showed that HBOT therapy reduced the overall amputation rate by 24% (95% CI: 14%, 33%) compared with the control group. For other study types, a hypothetical control group with a 50% amputation rate was assumed, and HBOT therapy was found to result in a reduction in amputation incidence of 32% (95% CI: 21%, 44%).

Proportion of wounds healed

Based upon the data from two RCTs, Roeckl-Wiedmann et al.\(^40\) showed that the proportion of wounds that had healed by 2 weeks after therapy did not differ significantly between the HBOT and control groups. Further outcome assessments at 6 weeks and 6 months also showed no evidence of a statistically significant difference. One small trial showed a statistically significant increase in the proportion of wounds healed for the HBOT group (RR=2.3; 95% CI: 1.1, 4.6) 1 year after treatment. However, this result was sensitive to the effects of patient withdrawal from the study. In a meta-analysis of two controlled trials, MSAC\(^8\) reported the odds of wound healing in the HBOT treated group to be 40 times greater than in the control group (odds ratio [OR]=39.39; 95% CI: 5.54, 280.32).

Reduction in wound size

Roeckl-Wiedmann et al.\(^40\) reported non-significant differences in wound size reduction comparing the HBOT and control groups, immediately after and 4 weeks after treatment. These results were based on one small RCT.

Other outcomes

The MSAC\(^8\) study also reported a non-statistically significant reduction in length of hospital stay in HBOT patients compared with the control group. As length of stay data is influenced by many factors, these results are of limited relevance to the UK treatment setting.

Predictors of outcomes

The study by Fife et al.\(^53\) used multivariate modelling to investigate potential factors affecting the success or failure of HBOT. Factors significantly related to outcome included renal failure, pack-year smoking history, transcutaneous oximetry, number of HBOT treatments and interruption of the treatment regimen.

Adverse events

A retrospective case series\(^54\) included in the ECRI\(^47\) analysis, examined the records of 54 patients with lower extremity wounds treated in one USA centre from 1989–1994. The authors noted that 23 patients experienced barotraumas, 5 patients symptoms of claustrophobia and 1 patient a seizure. One RCT\(^57\) reported that 2 of 35 patients experienced barotraumas, though treatment interruption was not required.

Discussion

Drawing conclusions on the applicability of HBOT to diabetic lower extremity ulcers is limited by a lack of quality evidence. The results of the Roeckl-Wiedmann et al.\(^40\) meta-analysis and supporting evidence from other reviews suggest that HBOT significantly reduces the risk of major amputation in patients with diabetic foot ulcers compared with standard care. It is noted that the finding that transcutaneous oxygen pressure around the ulcers is significantly raised following a course of HBOT supports a mechanism for this benefit\(^40\). A major potential bias regarding this finding however is whether the decision to amputate was made while treatment group allocation remained blinded. There is an indication that the incidence of minor amputation increases following HBOT. This may be because HBOT allows more limbs to be salvaged and these are then more susceptible to the need for minor amputation. As such this can be viewed as a positive outcome, though MSAC\(^8\) noted that evidence is not available to support this hypothesis.

For outcomes, such as the proportion of wounds healed and extent of healing, there is insufficient evidence to assess HBOT effectiveness. When significant benefits are reported for these outcomes, the findings are compromised by wide confidence intervals or the results not proving consistent on sensitivity analysis. The restricted amount of data available does not suggest that serious adverse events are likely.

As an early attempt at modelling factors related to HBOT outcome, the results of Fife et al.\(^53\) must be viewed as exploratory. The model was only able to account for 22.8% of the variation in HBOT treatment outcomes and no data were available to indicate reasons for variability in the control group. The results do, however, provide a starting point for further work to investigate which patients are most likely to benefit from HBOT.

There is a need to verify possible benefits of HBOT in diabetic foot ulcer treatment using a large RCT, using adequate follow-up intervals. The COST B14 RCT (www.oxynet.org/02COSTinfo/Public/DFL_Protocol.pdf) is currently underway and should add to the evidence base on completion in 2008. An ulcer classification scheme, such as PEDIS (perfusion, extent, depth, infection, severity and sensation) which is currently being developed by the International Working Group on the Diabetic Foot (www.iwgdf.org), would ensure comparability of the data from different centres and studies.
Table 4.4.1 Evidence on using HBOT to treat diabetic lower extremity ulcers – included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim(s)</th>
<th>Search strategy/characteristic</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comment</th>
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<tr>
<td>Fife et al., 2007&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Retrospective cohort study</td>
<td>To report outcomes of patients receiving HBOT for diabetic lower extremity ulcers and to identify likely outcome predictors.</td>
<td>1,006 diabetic patients receiving treatment for lower extremity wounds in 5 Texas hyperbaric facilities. A further 139 patients were added to the dataset, after initial regression modelling, to validate the model.</td>
<td>The outcomes of 35 patients were not available. Renal failure patients (n=136) and patients receiving growth factor (n=194) were excluded from the final data set.</td>
<td>Number of HBOT treatments: coefficient=0.2087, p=0.0002 Transcutaneous oxygen in air: coefficient=0.004, p=0.0152 Pack years smoking: coefficient=-0.0035, p=0.0175 Maximal Wagner grade: coefficient=-0.1527, p=0.0003 Age and duration of diabetes: coefficient=-0.0041, p=0.0295 Interruption of treatment regimen: coefficient=-0.1907, p=0.0267</td>
<td>HBOT is an important adjunctive therapy for healing lower-extremity lesions, especially those of Wagner grade 3 or higher. Factors significantly related to HBOT outcome included: renal failure, pack-year smoking history, transcutaneous oximetry, number of treatments, and interruption of treatment regimen. No data were available concerning a control group.</td>
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<tr>
<td>Canadian Agency for Drugs and Technologies in Health (CADTH)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>HTA</td>
<td>To determine cost effectiveness of adjunctive HBOT versus standard care in Canadian patients with diabetic foot ulcers.</td>
<td>Comprehensive search of bibliographic databases, hand searching and identification of grey literature to 2005.</td>
<td>Controlled trials reporting outcomes in patients with diabetic foot ulcers treated with adjunctive HBOT and standard care only; patients of all ages with type 1 or 2 diabetes. Patients previously non-responsive to HBOT or improving with conventional therapy were excluded. Included studies RCTs: Abidia, 2003; Faglia, 1996; Doctor, 1992. Non-randomised comparative studies: Kalani, 2002; Faglia, 1998; Zambon, 1997; Baroni, 1987.</td>
<td>A summary of primary study outcomes as presented in terms of mean values from each study. The data were not combined. Patients with major amputations (7 studies): HBOT=11%, control=32% Patients with minor amputations (6 studies): HBOT=27%, control=15% Patients with healed wounds (6 studies): HBOT=83%, control=43% Patients with unhealed wounds (6 studies): HBOT=6%, control=24% Hospital stay in days (3 studies): HBOT=47.1, control=56.9 Adverse events: Two studies reported barotrauma (2 cases) and one study reported cataract (1 case).</td>
<td>There is evidence that HBOT is effective in the treatment of diabetic foot ulcers, but the small number of studies and their inadequacies were noted. A pragmatic approach for combining studies was adopted, with a view to providing input for economic analyses. No account was taken of disparate study size and nature.</td>
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<td>Study</td>
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<td>Gray &amp; Ratliff, 2006⁴⁵</td>
<td>Systematic review</td>
<td>Review the evidence on HBOT efficacy in the management of diabetic foot ulcers.</td>
<td>Comprehensive search of electronic databases and grey literature and reference list scanning. Search of databases from Jan 1966–Oct 2005.</td>
<td>Systematic reviews, meta-analyses, RCTs and quasi-experimental studies comparing HBOT and an alternative treatment. Case reports, case series and studies without English language abstracts were excluded.</td>
<td>Roeckl-Wiemann pooled some studies. The authors concluded that HBOT reduces the risk of major amputation in patients with diabetic foot ulcers. Wang et al. provided support that HBOT may be effective for chronic non-healing diabetic wounds. Results of the systematic review were not included in the conclusions as Wang et al. combined data from case series. The Kranke et al. results are reported below. All RCTs were included in at least one systematic review. Adverse events reported by Wang et al. 2001 included barotrauma, transient blurred vision (3 cases), seizures (23 cases), pneumothorax (1 case) and pulmonary oedema (3 cases).</td>
<td>Adjunctive HBOT improves the longterm likelihood of wound healing and reduces the risk of major amputation in patients with diabetic foot ulcers.</td>
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<td>Study</td>
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<td>Ministry of Health and Long-Term Care, 2005&lt;sup&gt;11&lt;/sup&gt;</td>
<td>HTA</td>
<td>To assess the effectiveness and safety of HBOT, for non-healing foot or leg ulcers in patients with diabetes.</td>
<td>Identified existing HTAs and systematic reviews. Carried out comprehensive electronic database searches (2003–2004) to update these.</td>
<td>Included RCTs of diabetic patients receiving HBOT as adjunctive therapy or alone. English language studies only. Outcomes: wound healing and amputation prevention. No new primary studies met the inclusion criteria and the study based its findings entirely on existing HTAs.</td>
<td>Results were reported individually for Roeckl-Wiedmann et al., 2005 and MSAC, 2000.</td>
<td>There is evidence that adjunctive HBOT is beneficial in patients with non-healing diabetic foot ulcers. However, the evidence quality is poor, limiting the weight that can be attached to the findings. There is a need for data from a well-conducted RCT with wound healing and amputation as primary endpoints before HBOT is widely utilised in patients with diabetic foot ulcers.</td>
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<sup>11</sup> HTA programme: Systematic Review 24.4.1 Diabetic lower extremity ulcers
| Study                      | Type                          | Aim(s)                                                                                                                                                                                                 | Search strategy/ characteristic                                                                                             | Indusion/exclusion criteria                                                                                           | Results                                                                                          | Conclusions and comment                                                                                                                                 |
|----------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Roeckl-Wiedmann et al., 2005 | Systematic review with meta-analysis | This study combined parts of the Cochrane review with new data from Kessler et al. | To assess the evidence and impact of HBOT in the management of chronic wounds (only diabetic wounds assessed here). | Included RCTs comparing adjunctive HBOT with no HBOT or sham therapy. Patients with chronic wounds associated with diabetes mellitus were included. Topical HBOT and animal studies were excluded. | Proportion of diabetic ulcers healed (HBOT versus control): Within 2 weeks (2 trials, n=46): RR=4.78 (95% CI: 0.94, 24.24). 6 weeks after treatment start (1 trial, n=18): RR=2.33 (95% CI: 0.92, 5.93). 6 months after treatment (1 trial, n=18): RR=1.8 (95% CI: 0.8, 3.9). 1 year after treatment (1 trial, n=18): RR=2.3 (95% CI: 1.1, 4.7). NNT=2 (95% CI: 1, 5). Results were sensitive to patient withdrawal. Wound size reduction: Immediately after treatment (1 trial, n=28): WMD=20.1 (95% CI: 4.26, 35.94). 4 weeks after treatment (1 trial, n=28): WMD=6.8 (95% CI: -9.8, 23.4). Risk of major amputation (3 trials, n=118): RR=0.31 (95% CI: 0.13, 0.71); NNT=4 (95% CI: 3, 11). Significance remained after sensitivity analysis. Risk of minor amputation (2 trials, n=48): RR=2.20 (95% CI: 0.58, 8.72). Adverse events (2 studies): Barotrauma (2 cases) No data on time to complete healing, rate of wound size reduction, quality of life or recurrence rate. | There is evidence that HBOT decreases the risk of major amputation in diabetes mellitus patients. No significant benefit was demonstrated on ulcer healing, wound area reduction or need for minor amputation. 5 small studies were included but were of variable quality. Inclusion criteria, eg severity and size of ulcer varied between trials, as did outcome measures. It was unclear whether the decision to amputate was made while blinded to treatment, this being a potential source of bias. The authors suggested that until good quality RCT evidence is available, HBOT may be used when other strategies have failed. |

There is evidence that HBOT decreases the risk of major amputation in diabetes mellitus patients. No significant benefit was demonstrated on ulcer healing, wound area reduction or need for minor amputation. 5 small studies were included but were of variable quality. Inclusion criteria, eg severity and size of ulcer varied between trials, as did outcome measures. It was unclear whether the decision to amputate was made while blinded to treatment, this being a potential source of bias. The authors suggested that until good quality RCT evidence is available, HBOT may be used when other strategies have failed.
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<td>ECRI, 2001[^47]</td>
<td>Systematic review with meta-analysis</td>
<td>To provide an overview of HBOT in chronic wound treatment (only diabetic wounds assessed).</td>
<td>Comprehensive search of electronic databases and grey literature, bibliography scanning, hand searching of journals. No lower date limit was applied and the upper date limit varied between databases. Generally literature to early 2001 was included.</td>
<td>HBOT therapy for diabetic foot wounds. Outcomes: number of wounds healed, change in wound size, time to wound healing and number of amputations. <strong>Included studies</strong> RCTs: Faglia et al., 1996; Doctor et al., 1992. Prospective controlled trials: Faglia et al., 1998; Oriani et al., 1990; Baroni et al., 1987. End stage: Lee et al., 1997; Wattel et al., 1991; Cianci et al., 1988. Case series: Ciaravino et al., 1996; Davis, 1987.</td>
<td>Meta-analysis of 2 RCTs and three controlled trials Difference in amputation rate between HBOT and control = 0.24 (95% CI: 0.14, 0.33; p=0.000001). Test for heterogeneity Q=1.33, p=0.856. Meta-analysis of 3 end-stage studies, using a hypothetical control group with 50% amputation rate. Difference in amputation rate between HBOT and control = 0.32 (95% CI: 0.21, 0.44; p=0.000001). Test for heterogeneity Q=0.66, p=0.719. Ciaravino et al. 1996 reported 23 of 54 patients with barotrauma; 5 of 54 patients with claustrophobia; 1 of 54 patients with seizure.</td>
<td>HBOT is effective at reducing amputation rate in patients with severe diabetic foot ulcers. The results of the end stage meta-analysis are highly dependent on the choice of amputation rate for the control group. This will depend on wound severity but the reporting on this parameter was minimal. Standardisation of treatment protocols (pressure, length of session, number of sessions and stage of diabetic foot ulcer) was needed.</td>
</tr>
<tr>
<td>Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé, 2001[^11]</td>
<td>HTA</td>
<td>To review the efficacy of HBOT treatment of a number of conditions (only diabetic wounds assessed here).</td>
<td>Limited electronic database search. Scanning bibliographies. Literature in databases to July 1999 used.</td>
<td>Studies in English or French. <strong>Included studies</strong> RCTs: Faglia et al., 1998; Doctor et al., 1992. Controlled trials: Stone et al., 1998.</td>
<td>Study results reported separately. No attempt made to pool or synthesise data.</td>
<td>HBOT can have a beneficial effect on diabetic wounds, however these results need to be confirmed in RCTs.</td>
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[^47]: ECRI, 2001
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<tr>
<td>Medical Services Advisory Committee, 2001*</td>
<td>HTA</td>
<td>To evaluate HBOT safety and effectiveness for the treatment of diabetic wounds.</td>
<td>Electronic database search, attempts to identify grey literature, expert opinion and reference list scanning. Covered literature from 1966–1999.</td>
<td>Included studies of HBOT in mono- or multiplace chambers, with a control group and published in English. <strong>Included studies</strong> RCTs: Faglia, 1996; Doctor, 1992. Controlled trials: Faglia, 1998; Zamboni, 1997; Baroni, 1987.</td>
<td>Risk of major amputation in HBOT patients compared with controls (5 studies): OR=0.25 (95% CI: 0.13, 0.5). Significance was maintained in sensitivity analysis. Absolute reduction in risk of amputation: AR=20% (95% CI: 11%, 30%), NNT=5 (95% CI: 3.3, 9.1). Risk of minor amputation (3 studies): OR=1.76 (95% CI: 0.68, 4.59). Absolute reduction in risk of minor amputation: AR=9% (95% CI: -8, 25%). Wound healing (2 studies): OR=39.39 (95% CI: 5.54, 280.32). Risk of wound healing (38 patients, two controlled trials): OR=39.39 (95% CI: 5.54, 280.32; p&lt;.001). Length of hospital stay (2 studies): Study 1 a reduction of 19 days and study 2 a reduction of 6.4 days (neither were statistically significant).</td>
<td>Major amputations were less likely in those receiving HBOT. There was some indication that HBOT promoted wound healing and reduced length of hospital stay but increased the risk of minor amputation.</td>
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<td>Study</td>
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<tr>
<td>O'Meara et al., 2000</td>
<td>HTA</td>
<td>To estimate the clinical effectiveness of interventions for the prevention and treatment of diabetic foot ulcers.</td>
<td>Comprehensive electronic database search, attempts to identify grey literature, bibliography scanning, expert opinion and hand searching. Databases searched to Jan 2000.</td>
<td>RCTs in any language that evaluated HBOT for the prevention or treatment of diabetic foot ulcers. If no RCTs were available, controlled trials could be included. Outcomes: Primary: wound healing, prevention of wound formation, change in ulcer size, rate of healing, frequency of complete healing and time to complete healing. Studies were assessed for methodological quality using a checklist. Included studies RCTs: Faglia, 1996; Leslie et al., 1988 (topical HBOT not included).</td>
<td>2 RCTs evaluated the effectiveness of HBOT for treating diabetic foot ulcers. Faglia 1996 Risk of major amputation in treatment group versus control: OR=0.22 (95% CI: 0.07, 0.72). Risk of minor amputation in treatment group versus control: OR=2.54 (95% CI: 0.99, 6.53). Leslie 1988 No significant differences were found in change in ulcer area or depth.</td>
<td>Without data on quality of life, limb function and cost effectiveness it is impossible to draw firm conclusions.</td>
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<td>Study</td>
<td>Type</td>
<td>Aim(s)</td>
<td>Search strategy/characteristic</td>
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<td>Wunderlich et al., 2000</td>
<td>Systematic review</td>
<td>To document the literature on HBOT as an adjunct to standard lower extremity wound care, focusing on diabetic foot.</td>
<td>Search of MEDLINE database and reference list scanning.</td>
<td>Included English language studies only. Included studies RCTs: Faglia, 1996; Doctor, 1992. CTs: Zamboni, 1997; Oriani, 1990; Baroni, 1987. Other studies: Oriani, 1992; Wattel, 1991.</td>
<td>Reported the results of individual studies separately. These studies were included in later systematic reviews.</td>
<td>HBOT can reduce the number of major amputations in patients with Wagner grade IV wounds. Further RCT evidence is required to confirm these results and inform on other outcomes.</td>
</tr>
<tr>
<td>Kaltenthaler et al., 1998</td>
<td>Systematic review</td>
<td>To critically review evidence on the effectiveness of interventions for diabetic foot ulcers.</td>
<td>Comprehensive electronic database search, identifying grey literature and hand searching. Studies published 1986–1996.</td>
<td>Included English language RCTs only. Included studies RCTs: Faglia, 1996; Doctor, 1992; Leslie, 1988 (topical HBOT, not considered).</td>
<td>Reported the results of individual studies separately. These studies were included in later systematic reviews.</td>
<td>HBOT shows promise for severe foot ulcers but the need for further research was highlighted.</td>
</tr>
<tr>
<td>Mitton &amp; Hailey, 1998</td>
<td>HTA</td>
<td>To detail evidence on effectiveness of HBOT, and the possible impact on health care of establishing a second HBOT facility in Alberta.</td>
<td>Literature search of electronic databases, reference list scanning and expert opinion. Searched up to 1997.</td>
<td>Included studies considered to be of the highest evidence level for diabetic leg ulcers. Included studies RCTs: Faglia, 1996; Doctor, 1992. CT: Baroni, 1987.</td>
<td>Reported the results of individual studies separately. These studies were included in later systematic reviews.</td>
<td>There is strong evidence to support the use of HBOT for the treatment of diabetic leg and foot ulcers.</td>
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NNT = number needed to treat, WMD = weighted mean difference, AR = absolute risk
4.4.2 Cardiac neural regulation dysfunction

The literature search identified one RCT that assessed the effect of HBOT on cardiac neural regulation dysfunction in patients with diabetic foot problems⁵⁹, as presented in Table 4.4-2. Changes in heart rate variability parameters were measured from baseline over the 4-week study period. Based on statistically significant vagotonic effects, the authors concluded that HBOT is beneficial in wound management and attenuates autonomic neuropathy and enhances quality of life in patients with diabetes mellitus. No indication was given of randomisation method, blinding of outcome assessment or measurement of clinical outcome.
### Table 4.4.2 Evidence on using HBOT to treat cardiac neural dysfunction in patients with diabetic foot ulcers - included studies

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<th>Study</th>
<th>Type</th>
<th>Aim(s)</th>
<th>Search strategy/ characteristic</th>
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<tr>
<td>Sun et al., 2006⁷⁵</td>
<td>RCT</td>
<td>To test the hypothesis that adjunctive HBOT may restore cardiac neural regulation in patients with diabetic foot.</td>
<td>38 adults (mean age 60 years) with type 2 diabetes and foot complications. HBOT: 100% O₂, 202.65 kPa, 90 mins, 5 days a week for 4 weeks (20 sessions). Control: no HBOT</td>
<td>Hospital-based patients referred for surgical management of foot complications. Exclusion criteria: cardiac pacemaker, arrhythmia, septic shock, congestive heart failure, acute myocardial infarction or cerebrovascular accident immediately before or during the study, indication for repeat anaesthesia, failure of wound control and progression to amputation.</td>
<td>There was a statistically significant difference in change of heart rate parameters (RR interval, HF, LF) in favour of HBOT at 1, 2, 3 and 4 weeks follow up (p&lt;0.05). Local tissue oxygenation was significantly higher in the HBOT group (p&lt;0.05).</td>
<td>HBOT had a significant vagotonic effect, which was beneficial at improving cardiac neural regulation in patients with diabetic autonomic dysfunction. The randomisation method was not reported and outcome assessment was not blinded.</td>
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</table>
4.4.3 Non-diabetic wounds

Evidence identified

Five systematic reviews\(^{6,40,47,48,60}\) and six HTAs\(^{8,10-12,62,63}\) were identified that covered this indication. These studies were undertaken from 1998–2006 in the UK, Canada, the USA and Australia and details are presented in Table 4.4.3. The 11 secondary studies mostly considered the same restricted number of primary studies, with highly variable patient groups, treatment regimens and outcomes. The reviews and HTAs all presented the individual primary study findings separately, with no attempt being made to synthesise the data. The results of the individual primary studies is reported only once in our data extraction, as a component of the most recent secondary study. The data presented for each primary study may, however, have been taken from several secondary sources. Two evidence based guidelines were also identified\(^ {44,65}\), which briefly mentioned HBOT but were based on the same primary studies.

No additional controlled trials, undertaken after the completion of the latest secondary study, were identified. An interim analysis from an ongoing Australian cohort study\(^ {44}\) and 10 case series\(^ {61,66-74}\) were retrieved. Data extraction was not undertaken for the cohort study as it was incomplete or for the case studies as they were of insufficient quality to add to the existing evidence base.

Evidence quality

In general the HTAs and systematic reviews carried out comprehensive searches to identify evidence, and reported study inclusion and exclusion criteria for the selected studies. ECRI\(^ {62}\) and Friedman et al.\(^ {66}\) failed to report their evidence sources and Friedman et al., did not report the inclusion criteria used. Literature searches undertaken by AETMIS\(^ {10}\) and Mitton and Hailey\(^ {11}\) were very limited. Most reviews restricted themselves to English language or English and French studies\(^ {10}\), although some included studies in all languages\(^ {12,40}\), RCTs in all languages\(^ {63}\) or studies with English abstracts\(^ {45}\). Most reviews only considered controlled trials, though some\(^ {10,47,48}\) included all study designs. MSAC\(^ {63}\) included case series where patients were consecutively enrolled and Mitton and Hailey\(^ {11}\) included studies of the highest evidence level available for the particular indication. In spite of the differing inclusion criteria most reviews covered the same primary studies, so variations in methodological quality were not of major concern.

The main issue for all HTAs and reviews was the limited quantity and quality of the primary literature. Few controlled trials were identified and those available included small patient numbers, suffered from inadequate reporting and were all carried out more than 10 years ago.

Synthesis of these primary data was compromised by variable study entry criteria (in terms of wound severity, aetiology, and duration and extent of complicating infection), differences in treatment regimens and the extent of blinding. The comparator treatment in most studies was ‘standard wound care’ but the exact meaning of the term differed between studies. In some instances the comparator was placebo HBOT.

Results

Patient-related outcomes varied between studies but included: the proportion of wounds healed, changes in the size of the wound area, time to healing, duration of hospitalisation, amputations avoided, additional surgery required and wound infection. Adverse events were also considered.

Given the differences in the aetiology of the wounds considered in this section, the results are presented separately for each wound type.

4.4.3.1 Venous ulcers

Eight secondary studies\(^ {8,10,11,40,45,47,48,63}\) reported an RCT undertaken by Hammarland and Sundberg in 1994. The secondary studies reported this RCT to show that, though there was no statistically significant increase in the proportion of ulcers healed in the HBOT group (RR=1.33; 95% CI: 0.89, 1.99), patients managed with HBOT experienced significantly greater reductions in mean wound area than the control group at 4 (22% ± 13% versus 3.7% ± 11%; p=0.0088) and 6 weeks (35.7% ± 17% versus 2.7% ± 11%; p=0.0004).

The reviews noted that this was a very small RCT, in which the randomisation process was inadequately described, concurrent treatments were not reported and only limited patient characteristics were provided. As such the results should be viewed with some caution. In addition, patients in this study had larger wounds than normally seen and, consequently, the results may not be generalisable.

Two case series were included by ECRI\(^ {62}\) but, in the absence of a control group and given the poor reporting, these did not add to the evidence base.

On the basis of the small amount of available data, about half of the secondary studies concluded that there is insufficient evidence to determine whether HBOT plus standard care is more effective than standard care alone. Other studies interpreted the results as sufficient to indicate benefit for HBOT in the healing of chronic venous ulcers.

4.4.3.2 Pressure ulcers

Gray & Ratliff\(^ {45}\), MSAC\(^ {63}\) and ECRI\(^ {62}\) all reported a study by Rosenthal and Schurman (1971). They reported that 22 of 38 pressure ulcers healed completely in the group receiving HBOT and 5 of 38 reduced in size by >50%. In the small control group 0 of 6 ulcers healed or reduced in size by >50%.

The generalisability of these results is limited as the study was small, and lacked randomisation and comparison of demographic and wound characteristics between treatment and control groups. Consequently the three
reviews all concluded that it is unclear whether HBOT plus standard care is more effective than standard care alone for treating pressure ulcers.

4.4.3.3 Other chronic wounds

MSAC reported a controlled trial of HBOT in women facing wound breakdown following vulvectomy. While the results appeared favourable towards HBOT, the study was of low quality and MSAC did not consider it to provide support for the effectiveness of HBOT in this indication.

4.4.3.4 Crush injuries

ECRI, Wang & Lau, AETMIS, MSAC, Saunders and Mitton & Hailey all reported the RCT undertaken by Bouachour et al. Various outcomes were considered in this study, with a statistically significant improvement being seen in the likelihood of complete healing in patients treated with HBOT plus standard care compared with standard care alone (RR=1.7; p<0.01).

ECRI also reported a retrospective case controlled study undertaken by Radonic et al. in 1995. Analysis of the results did not show a statistically significant difference in the likelihood of amputation between the HBOT and control groups. However, it was noted that patients receiving HBOT had more serious wounds, biasing the study against HBOT.

ECRI suggested that patients whose crush injuries were treated with HBOT may have a lower incidence of amputation than those receiving standard care. However, the earlier reviews were of the opinion that there is insufficient evidence to determine the effectiveness of HBOT as an adjunct to standard care.

4.4.3.5 Blunt chest injury

A retrospective case series analysed outcomes from 26 patients with severe blunt chest injury who received adjunctive HBOT or conventional treatment alone. The authors concluded that early HBOT can significantly increase the survival rate.

4.4.3.6 Calciphylaxis (calcific uremic arteriopathy)

None of the systematic reviews or HTAs considered the use of HBOT for calciphylaxis. Two case series, making brief mention of HBOT, were identified by a literature search undertaken to update the AHRQ report. Given the lack of evidence it is impossible to draw any conclusions on the use of HBOT for this indication, and well designed trials are required to establish efficacy.

4.4.3.7 Grafts and flaps

One systematic review was exclusively concerned with skin grafts and flaps. Four other secondary studies also considered skin grafts. Composite grafts

Only case studies were identified by Friedman et al. While these studies reported successful grafting with adjunctive HBOT, in the absence of a control group the results are inconclusive.

Skin grafts

The secondary literature comprised two RCTs on skin grafts. The RCT by Perrins reported that HBOT significantly improved grafting compared with standard care. However, Friedman et al. noted that technological developments mean that these results are no longer relevant. Marx reported significant benefits with HBOT, however study quality was considered poor and reporting inadequate.

Flaps

Case series indicated improved flap recovery rates with adjunctive HBOT, however the studies were poorly conducted and lacked controls. The results were, therefore, considered of limited value in evaluating efficacy.

Adverse events

The most recent review identified 10 studies which met their inclusion criteria for assessing adverse events. Of the 176 patients included in these studies, one unspecified serious complication occurred.

Discussion

Some improvements in wound healing are reported in studies identified in the secondary literature. However even when statistically significant benefit was achieved, the findings were compromised by the studies being small, of low quality and the reporting being inadequate. The evidence available was not of sufficient quality to determine whether adjunctive HBOT is effective for treatment of non-diabetic wounds in comparison with standard care alone.

Given the lack of clarity over the use of HBOT in this setting, it is surprising that no controlled studies have been undertaken since 1996. One ongoing RCT examining the use of HBOT for severe lower limb trauma was identified by ECRI, however this will not complete until 2010. Future controlled trials should ensure that patients in treatment and control groups: have wounds of comparable size, severity and aetiology; have similar demographic characteristics; receive standardised intervention and comparator treatments at similar time periods; and measure standardised outcomes at prespecified time periods.

Some reviews suggested that while evidence supporting the effectiveness of HBOT is lacking the main alternative for these patients, often amputation, is so unpleasant that HBOT should be offered where available. Caution is required however as amputation is not always necessary, and though HBOT results in few adverse events it is not completely without safety concerns.
Table 4.4-3 Evidence on using HBOT to treat non-diabetic wounds - included studies

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<th>Study</th>
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<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
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<tr>
<td>ECRI, 200662 Target report</td>
<td>Systematic review</td>
<td>Review evidence on the use of HBOT for acute soft-tissue injury (only non-diabetic wounds and crush injuries assessed)</td>
<td>Sources not listed.</td>
<td>Controlled trials in English with a least 10 patients (recently published as a full article). Animal studies excluded. 2 studies providing data on quality and efficacy of treatment were included. RCTs: Bouachour et al., 1996. Retrospective case controlled study: Radonic et al., 1995.</td>
<td>Bouachour et al. 1996: 36 patients with grade II or III lower limb injuries, surgical management within 6h of injury and no history of peripheral vascular disorders. <strong>Intervention</strong>: Standard therapy plus HBOT (90 mins of 100% oxygen at 2.5 ATA twice daily for 6 days). <strong>Control</strong>: Standard therapy plus sham HBOT consisting of ambient air (90 mins at 1.1 ATA 2x daily for 6 days). <strong>Results</strong> Complete healing: HBOT versus control RR=1.7 (p&lt;0.009). New surgical procedures: HBOT=2; control=8 (p=0.03). Amputation: HBOT 0 of 18; control 2 of 18. Wound dressings: HBOT 15.8 ±9.4; control 16.3±12.1 (p=0.45). Healing time (mean±SD) days: HBOT= 50.2±21.1; control=55.8 ±19.9 (p=0.21). Radonic et al. 1995: 28 soldiers who had suffered serious arterial war injuries. <strong>Intervention</strong> (n=13): HBOT plus standard treatment <strong>Control</strong> (n=15): standard treatment <strong>Results</strong> Amputations: ECRI analysis of the Radonic et al. data found no statistically significant difference between groups (p=0.17). Length of stay: ECRI analysis of Radonic et al. found that patients treated with HBOT underwent longer in treatment than controls (p=0.19).</td>
<td>The limited data suggest that patients treated with HBOT plus standard therapy may have a lower incidence of complete or partial amputation. 10 studies met the inclusion criteria for adverse events. In 176 patients there was one report of an unspecified serious complication. Patients, types of injury and treatment settings were different in the 2 studies so it was not possible to combine the results. Studies were small and no treatment effect was found.</td>
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<td>Study</td>
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<td>Gray &amp; Ratliff, 2006a</td>
<td>Systematic review</td>
<td>Review evidence on the efficacy of HBOT for management of lower extremity venous ulcer disease and pressure ulcers (diabetic wounds not assessed).</td>
<td>Comprehensive search of electronic databases, grey literature and reference list scanning. Included material added to databases from Jan 1966–Oct 2005.</td>
<td>Included systematic reviews, RCTs and quasi-experimental studies comparing HBOT with alternative treatment. Case reports and series, and studies without English language abstracts were excluded.</td>
<td>Lower extremity venous ulcers - Hammarland and Sundberg 1994: 16 patients, median age 67 years (range 42–75) with leg ulcers of &gt;1 year's duration and no healing progress in the 2 months prior to the study. Non-smokers with normal blood pressure and no chronic concomitant conditions. <strong>Intervention:</strong> 5 sessions per week in a multiplace HBOT chamber at 2.5 ATM for 90 mins for 6 weeks. <strong>Comparator:</strong> as above, but using 100% air. <strong>Results</strong> No significant increase in the proportion of ulcers healed in the HBOT group (RR=1.33; 95% CI: 0.89, 1.99). Patients managed with HBOT had significantly smaller mean wound area at 4 (22%±13% versus 3.7%±11% reduction; p=0.0088) and 6 weeks (35.7% ±17% versus 2.7%±11% reduction; p=0.0004) after treatment. Pressure ulcers - Rosenthal and Shurman 1971: 118 patients with 38 lesions, median age 41 (range 15–67). <strong>Intervention:</strong> 1.5h/day for 5 days/week, increased to 2h/day for 5 days/week. <strong>Results</strong> 22 of 38 ulcers healed and 5 of 38 reduced in size by &gt;50%. In the control group 0 of 6 ulcers healed or reduced in size. Lower extremity venous ulcers There is insufficient evidence to determine whether adjunctive HBOT is effective. The RCT was very small and the randomisation method was inadequately described. Pressure ulcers There is insufficient evidence to determine whether adjunctive HBOT is effective. Small study without randomisation or comparison of demographic or wound characteristics between groups.</td>
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<td>Roeckl-Wiedmann et al., 2005</td>
<td>Systematic review with meta-analysis</td>
<td>To assess evidence of efficacy for HBOT in the management of chronic wounds (diabetic wounds not assessed).</td>
<td>Comprehensive search of electronic databases to 2003, hand citation searching, reference list scanning and expert opinion.</td>
<td>RCTs compared adjunctive HBOT versus no HBOT/sham therapy. Topical HBOT and animal studies were excluded. Chronic wounds were those failing to heal with specific therapy that had not received HBOT. Wounds were associated with venous/arterial disease or external pressure. <strong>Included studies</strong> Hammarland and Sundberg, 1994.</td>
<td>Hammarland and Sundberg 1994: (reported above).</td>
<td>There is a lack of data on use of HBOT for venous, arterial or pressure ulcers.</td>
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| Friedman et al., 2006        | Systematic review | To establish whether there is evidence to demonstrate efficacy for HBOT when treating patients with compromised flaps and grafts. | Methodology for identifying studies was not reported.                                      | Inclusion criteria were not reported. Included studies: Composite grafts
- Case reports: Gonnering et al., 1986; Nichter et al., 1991; Rapley et al., 2001; Friedman et al., 2003.
- Skin grafts
- Random flaps
  - Case series: Perrins, 1975; Bowersox et al., 1986; Ueda et al., 1987; Schweitzer and Burtka, 1990.
- Distant flaps
  - Case study: Ueda et al., 1987.
- Free flaps
  - No studies.                                                                 | Composite grafts:
  - All case studies reported successful grafting with adjunctive HBOT.
  - Skin grafts, Perrins 1967:
    - 24 patients received HBOT postoperatively, 24 control patients did not receive HBOT.
      - Intervention: HBOT for 2h on the evening of the operation and twice/day for 3 days at 2 ATA.
      - Results:
        - Complete graft take occurred in 64% of HBOT treated patients and 17% of controls; RR=3.8%; p<0.01.
  - Random flaps, Perrins 1975:
    - Flap failure rate reduced to 4.5% following use of HBOT (from 8.5–11.8% in the 5 preceding years).
  - Bowersox et al. 1986:
    - Incomplete result reporting was noted.
  - Ueda et al. 1987:
    - Average flap recovery rate was 92.1% though there were major variations in treatment regimens between patients.
    - Schweitzer and Burtka 1990:
      - No useful results.
      - Distant flaps
        - No useful results.                                                                 | HBOT may have efficacy in supporting the take of relatively large composite grafts. The evidence was limited and of poor quality with no indication of the methodology used to identify the literature.
S There is no evidence to demonstrate improved skin graft survival with preoperative HBOT. Technological advances mean the results of the 1967 RCT are no longer relevant.
S There is insufficient evidence to determine usefulness with random flaps. HBOT may increase the amount of surviving tissue in an ischemic flap that could become necrotic.
S There is insufficient evidence to determine the usefulness of HBOT for distant flaps.
S Most evidence is from case series reports.
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<tr>
<td>Medical Services Advisory Committee, 2003</td>
<td>HTA</td>
<td>To evaluate the safety and effectiveness of HBOT in managing non-healing wounds in non-diabetic patients (other indications not assessed here).</td>
<td>Comprehensive search of electronic databases, grey literature, reference list scanning and expert opinion. Included literature published from 1966–2002.</td>
<td>Included non-diabetic patients with non-healing, refractory wounds, having failed on conventional therapies. HBOT versus standard care placebo procedures. All study types used, though case series were only included if the patients were enrolled consecutively or presented within a specific time frame. RCTs and systematic reviews in all languages; other study designs in English; all relevant patient outcomes.</td>
<td>Hammarland and Sundberg, 1994 (reported above). Reedy et al. 1971: Women with or without wound breakdown (from medical records) following radical vulvectomy (n=8), who had surgery for the indication but not HBOT. Age 13–98 years. <strong>Outcomes</strong>: Length of hospitalisation, wound breakdown, infection. <strong>Results</strong>: With lymph node dissection Intervention - 1 of 6 cases of wound breakdown and 1 of 6 of infection; Control - 7 of 9 cases of wound breakdown and 4 of 9 of infection. Without lymph node dissection Intervention - 0 of 2 cases of wound breakdown and 0 of 2 of infection; Control - 3 of 13 cases of wound breakdown and 1 of 13 of infection. Length of hospitalisation was shorter for patients in HBOT group where wound breakdown did not take place.</td>
<td>The clinical evidence was inadequate to substantiate claims that HBOT is effective in the treatment of non-diabetic refractory wounds. As there are no effective alternative therapies and in view of progress in local data collection and an international trial, funding should continue for 3 years. The 2 included trials were of low methodological quality.</td>
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<td>Wang &amp; Lau, 2001^4</td>
<td>Systematic review</td>
<td>To determine whether HBOT is an effective adjunctive treatment for hypoxic wounds (diabetic wounds not assessed).</td>
<td>Existing systematic reviews were identified and the literature included in these updated by a MEDLINE search for articles published from mid 1998–Aug 2001. Expert peer reviewers were asked to suggest papers.</td>
<td>Included published articles with ≥5 patients in English. All study designs. <strong>Included studies</strong> HTAs: Saunders, 2000; Villanueva, 2000; Blue Cross Blue Shield, 1999 Mitton and Hailey, 1998. Acute traumatic peripheral ischemia Case study: Mathieu, 1990. Crush injuries and suturing of severed limbs RCT: Bouachour, 1996. Compromised skin grafts RCTs: Marx, 1995; Perrins, 1967. Chronic non-healing wounds RCT: Hammarlund and Sundberg, 1994.</td>
<td>HTAs reported individually (see appropriate sections of this table). Acute traumatic peripheral ischaemia: no patient-related outcomes reported. Crush injuries and suturing of severed limbs Bouachour et al., 1996: (reported above). Compromised skin grafts Marx et al. 1994: Wound infection - HBOT versus control RR=0.25. Wound dehiscence - HBOT versus control RR=0.23; p=0.001. Delayed wound healing: HBOT versus control RR=0.2; p=0.001. Chronic non-healing wounds: Hammarlund and Sundberg, 1994 (reported above).</td>
<td>There is sufficient objective evidence that HBOT aids wound healing for compromised skin grafts and chronic non-healing wounds. The overall evidence quality was poor with inadequate or no control group for most studies.</td>
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<td>ECRI, 2001†</td>
<td>Systematic review with meta-analysis</td>
<td>To provide evidence for use of HBOT in the treatment of chronic wounds (diabetic wounds not assessed).</td>
<td>Comprehensive search of electronic databases, grey literature, bibliography scanning and hand searching of journals. Generally literature available prior to early 2001 was included.</td>
<td>Studies using HBOT for pressure ulcers, or venous or arterial leg ulcers. All study designs.</td>
<td>Pressure ulcers: Rosenthal and Schurman, 1971 (reported above). Venous leg ulcers: Hammarland and Sundberg, 1994 (reported above). Bass, 1970: 17 of 19 wounds healed. Change in size was not reported. Mean time to healing was 35.8 days. Yephuny, 1985: 74% of patients had satisfactory to good treatment results.</td>
<td>Most trials did not adequately report wound size, wound stage, concurrent treatments (e.g. dressing type, antibiotic use), change in wound size and mean time to wound healing. Pressure ulcers No control group and no reporting of wound severity. Provided little evidence on the use of HBOT. Venous leg ulcers There is insufficient evidence on the extent to which HBOT can be used to treat venous leg ulcers. The RCT failed to report concurrent treatment and gave few patient characteristics. Wound size was large for this type of ulcer. Small sample size and the nature of the wounds precluded generalisation. Case series lacked a control group and reported wound characteristics poorly, the results could not be generalised.</td>
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<td>Crush injuries: Bouachour et al., 1996.</td>
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<td>Medical Services Advisory Committee, 2001¹¹</td>
<td>HTA</td>
<td>To evaluate HBOT in terms of safety and effectiveness for the treatment of non-diabetic wounds, skin grafts and crush injuries (other indications not assessed here).</td>
<td>Electronic database search, grey literature, expert opinion and reference list scanning. Covered the literature from 1966–1999.</td>
<td>Included studies of HBOT in mono- or multiplace chambers, with a control group. Studies published in English.</td>
<td>Reported the results of studies separately.</td>
<td>Non-diabetic wounds: There was some evidence of effectiveness but based on a small number of patients and one outcome measure.</td>
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<td>Crush injuries: Bouachour et al., 1996.</td>
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<td>Saunders, 2000&lt;sup&gt;12&lt;/sup&gt;</td>
<td>HTA</td>
<td>To review the clinical effectiveness of HBOT and determine whether there is a business case for an HBOT unit in the West Midlands (only non-diabetic wounds, skin grafts and crush injuries assessed).</td>
<td>Comprehensive search of electronic databases, expert opinion and reference list scanning. Sources searched from 1968, with no upper date limit reported.</td>
<td>Studies on patients with relevant indications receiving HBOT. All languages and all study designs included. Skin grafts RCT: Perrins, 1967. Crush injury RCT: Bouachour et al., 1996.</td>
<td>Skin grafts: Perrins, 1967 (reported above). Crush injury: Bouachour et al., 1996 (reported above).</td>
<td>While there is insufficient evidence to justify the use of HBOT for crush injuries or skin grafts, further investigation is warranted.</td>
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4.4.3 Non-diabetic wounds
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<td>Mitton &amp; Hailey, 1998</td>
<td>HTA</td>
<td>To detail evidence on the effectiveness of HBOT for non-diabetic wounds, skin flaps and grafts (other indications not assessed).</td>
<td>Limited electronic database search. Searched to various dates in 1997.</td>
<td>Studies considered were those of the highest evidence level for each indication.</td>
<td>Leg ulcers: Hammarlund and Sundberg, 1994 (reported above). Skin flaps and grafts: Perrins, 1967 (reported above); Bowersox, 1986 (reported above). Kindwall et al., 1991 - increased graft survival when HBOT included in regimen. Crush injuries: Bouachour et al., 1994 (reported above).</td>
<td>There is some evidence to support the use of HBOT for chronic leg ulcers. Skin flaps/grafts Evidence on the use of HBOT is unclear. Crush injuries Evidence on the use of HBOT is unclear.</td>
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<td>Study</td>
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<td>Rogatsky &amp; Mayevsky, 2007</td>
<td>Retrospective case series</td>
<td>To investigate the effect of adjunctive HBOT in patients with severe blunt chest injury.</td>
<td>26 patients with severe blunt chest injury receiving conventional treatment who developed arterial hypoxaemia within 24–72h of injury. HBOT: O₂, 1.6-2.0 ATA, 40–60 min per day for 4–15 consecutive days. Control: conventional treatment. Outcomes: cardiac output index, stroke volume index, arterial blood gas.</td>
<td>Patients receiving conventional treatment who developed arterial hypoxaemia within 24–72h of injury.</td>
<td>Statistical comparisons were made between survivors who received conventional treatment (n=4), those who died after receiving conventional treatment (n=4) and survivors treated with combined HBOT and conventional treatment (n=8). The HBOT group showed earlier and more significant normalisation of monitored parameters compared with survivors who received conventional treatment.</td>
<td>Early application of HBOT lowers mortality from severe blunt chest injury.</td>
</tr>
</tbody>
</table>
4.5 Necrotising soft-tissue infections and dermatology

This section covers the use of adjunctive HBOT in the treatment of various types of soft-tissue and surgical-site infections, and livedoid vasculopathy.

4.5.1 Necrotising soft-tissue infections

Necrotising soft-tissue infections constitute a spectrum of severe bacterial infections that can involve the skin, subcutaneous fat or muscle. Gas gangrene, also known as clostridial myonecrosis, is caused by the toxin and gas producing *Clostridium* bacteria. Necrotising fasciitis is commonly a result of infection by haemolytic *Streptococcus* and *Staphylococcus aureus* bacteria, either alone or acting together. However, other aerobic and anaerobic pathogens may be present. Where this condition affects the genitals or perineum, it is known as Fournier’s gangrene. Treatment for necrotising soft-tissue infections involves surgical debridement of all necrotic tissue, use of appropriate antibiotics, good nutritional support and optimal oxygenation of the infected tissue. Adjunctive HBOT has been used for increasing tissue oxygenation.

Evidence identified

A systematic review of HBOT for necrotising fasciitis or Fournier’s gangrene included three studies that retrospectively compared groups of patients who received adjunctive HBOT with those who received standard care: one in patients with necrotising fasciitis, one in patients with Fournier’s gangrene and one in patients with various truncal necrotising infections including both former conditions. An earlier systematic review undertaken for an Australian HTA identified the same studies and included two additional reports: one comparing patients with necrotising fasciitis, Fournier’s gangrene or gas gangrene versus historical controls, and a retrospective comparison of patients with necrotising fasciitis versus concurrent controls. A further HTA identified two review articles and one study in which patients with gas gangrene were treated with HBOT and efficacy was compared with that in historical controls not treated with HBOT. The studies included in the three reviews were published from 1985–1998. An updated search identified one retrospective case series of patients with necrotising fasciitis published in 2005 which, due to the absence of a comparator group, was not considered further. The supporting evidence from these reports is summarised in Table 4.5.1.

Evidence quality

The rapid systematic review and the MSAC study were both well conducted. The literature searches were sufficiently extensive to identify relevant studies published up to mid-2002, although one review restricted inclusion to studies published in English. The commonality between the studies included in both reviews is reassuring, though the possibility that publication and language bias could have favoured identification of studies with positive results cannot be ruled out. The Canadian HTA provided little detail of the methodology used, making it difficult to assess the robustness of the findings. No RCTs, controlled trials or well-designed cohort studies were identified by any of the reviews. The evidence consisted of small retrospective studies that did not control for selection bias between HBOT and comparator groups. Both reviews concluded that serious design flaws in all of the component studies limited the reliability of the findings.

Results

Two studies of patients with various necrotising soft-tissue infections retrospectively compared survival among those who received adjunctive HBOT (n=30) versus concurrent controls (n=24) or those who received adjunctive HBOT (n=17) versus historical controls (n=12). Patient selection criteria and HBOT regimens differed between the studies. The latter study found a statistically significant survival benefit in the HBOT group compared with the historical controls. The other found no significant difference in survival, length of hospital stay or length of stay in intensive care, but did report significantly more operations and debridements in the HBOT group.

Two studies reported on patients with necrotising fasciitis, retrospectively comparing adjunctive HBOT with standard care (25 versus 12 and 3 versus 8 patients respectively). Diagnosis was based on clinical signs and symptoms; only one study described the HBOT regimen. No statistically significant difference in survival was seen in either study. The larger study also found no significant difference in length of hospital stay, but found that the mean number of debridements was significantly lower in the comparator group.

One retrospective study that compared 14 men with Fournier’s gangrene who received adjunctive HBOT over a 6-year period versus 12 men who had not found a statistically significant survival difference in favour of HBOT. A study of patients with gas gangrene reported reduced mortality in the HBOT group compared with historical controls, but values were not presented.

No adverse effects data were reported.

Discussion

Evidence available in the published literature is inconsistent and of insufficient quality to provide reliable conclusions on the benefits of adjunctive HBOT for necrotising soft-tissue infections such as necrotising fasciitis, Fournier’s gangrene and gas gangrene.
### Table 4.5-1 Evidence on using HBOT to treat soft tissue infection - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Services Advisory Committee, 2001</td>
<td>Technology assessment report</td>
<td>To evaluate the safety and effectiveness of HBOT in general necrotising soft-tissue infections.</td>
<td>MEDLINE, HealthSTAR, EMBASE, The Cochrane Library, CINAHL, Nursing collection, biological abstracts, best evidence, HTA group websites, database of RCTs in Diving and Hyperbaric Medicine (DORCTHIM), secondary references, books, hand searching and expert opinion. Quality was assessed for internal and external validity and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence.</td>
<td>Studies of patients with necrotising soft-tissue infections were included. Studies were excluded if they were uncontrolled, did not have a comparison group or were not published in English.</td>
<td>2 non-randomised comparative studies, 1 using historical controls, were identified (Brown, 1994; Riseman, 1990). Neither reported blinding, both reported complete follow up. Clinical heterogeneity precluded meta-analysis. 1 study showed a statistically significant survival benefit for HBOT versus historical controls (43.1%; 95% CI: 9.7, 76.6; p=0.02) and the other no significant difference. Patients who received HBOT in 1 study underwent significantly more operations (mean 3.2±1.6 versus 1.7±1.5; p=0.0009) and debridements (mean 2.4 ±1.5 versus 1.3±1.0; p=0.003).</td>
<td>There is insufficient evidence to inform on robust, generalisable conclusions on the effect of HBOT in necrotising soft-tissue infections.</td>
</tr>
</tbody>
</table>

<p>| Medical Services Advisory Committee, 2001 | Technology assessment report | To evaluate the safety and effectiveness of HBOT for necrotising fasciitis. | MEDLINE, HealthSTAR, EMBASE, The Cochrane Library, CINAHL, Nursing collection, abstracts, best evidence, HTA group websites, DORCTHIM, secondary references, books, hand searching and expert opinion. Quality was assessed for internal and external validity and classified according to the NHMRC revised hierarchy of evidence. | Articles were excluded if they did not comply with one of the pre-agreed conditions, were uncontrolled, did not have a comparator group or were not published in English. | 2 non-randomised, retrospective comparative studies in adults were identified (Shupak, 1995; Barzilai, 1985). Neither reported blinding, both reported complete follow up. Clinical heterogeneity precluded meta-analysis. There was no statistically significant difference in survival for either study (16 of 25 versus 9 of 12; 2 of 3 versus 5 of 8). The larger study found no significant difference in length of hospital stay, but the mean number of debridements was significantly lower in the comparator group (1.5±0.8 versus 3.3±2.0; p=0.0004). | There is little firm evidence to support the use of HBOT for necrotising fasciitis. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Services Advisory Committee, 2001*</td>
<td>Technology assessment report</td>
<td>To evaluate the safety and effectiveness of HBOT for Fournier’s gangrene.</td>
<td>MEDLINE, HealthSTAR, EMBASE, The Cochrane Library, CINAHL, Nursing collection, biological abstracts, best evidence, HTA group websites, DORCHIM, secondary references, books, hand searching and expert opinion. Quality was assessed for internal and external validity and classified according to the NHMRC revised hierarchy of evidence.</td>
<td>Articles were excluded if they did not comply with one of the pre-agreed conditions, were uncontrolled, did not have a comparator group and were not published in English.</td>
<td>1 retrospective study of patient records was identified (Hollabaugh, 1998). 14 men with Fournier’s gangrene who had received adjunctive HBOT over a 6-year period were compared with 12 men who did not. A statistically significant difference in survival was noted in favour of HBOT (34.5%, 95% CI: 3.5, 65.6; p=0.037).</td>
<td>There was evidence of a survival benefit in patients with Fournier’s gangrene. More rigorous studies are required.</td>
</tr>
<tr>
<td>Bissett, 2002**</td>
<td>Evidence review</td>
<td>To summarise evidence on the effects of HBOT in patients with necrotising fasciitis or Fournier’s gangrene.</td>
<td>MEDLINE, EMBASE, The Cochrane Library, clinical evidence, NRR UK, NCI US, ISI SCI, Biosis, and DARE, HTA and NHS EED via the CRD website.</td>
<td>No explicit criteria were reported; language restrictions were unclear.</td>
<td>3 retrospective comparative studies were identified, 1 in necrotising fasciitis (Shupak, 1995), 1 in Fournier’s gangrene (Hollabaugh, 1998) and 1 in necrotising soft-tissue infections (Brown, 1994). Studies were all small and of weak design. Shupak, 1995 found no significant difference in death (36% versus 25%; p=0.71) or length of hospital stay (16 versus 20 days; p=0.41). Brown, 1994 found no difference in death (30% versus 42%) or length of hospital stay (32 versus 31 days). The HBOT group had a longer intensive care stay (7 versus 4 days) but the difference was not statistically significant. Hollabaugh, 1998 found no statistically significant difference in death (7% versus 42%; p=0.06).</td>
<td>There was no reliable evidence of HBOT benefit for necrotising fasciitis or Fournier’s syndrome. RCTs should be undertaken. All studies were included in the earlier MSAC report. The reviews differed in that one reported the number of survivors and the other deaths. There were some inconsistencies in the statistical analysis findings.</td>
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<tr>
<td>Study</td>
<td>Mitton &amp; Hailey, 1998</td>
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<tr>
<td>Type</td>
<td>HTA</td>
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<tr>
<td>Aim</td>
<td>To provide advice to the Calgary Region Health Authority on the effectiveness of HBOT and the impact of introducing an additional facility.</td>
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</tr>
<tr>
<td>Search strategy/characteristics</td>
<td>Comprehensive search of electronic databases, reference list scanning and expert opinion. Included studies to 1997.</td>
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<tr>
<td>Inclusion/exclusion criteria</td>
<td>Included the highest level of evidence available.</td>
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<tr>
<td>Results</td>
<td>Included 1 case series with historical controls and 2 review articles. Case series found less than 20% mortality in patients with HBOT compared with a 50% mortality when HBOT was not included.</td>
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<tr>
<td>Conclusions and comments</td>
<td>Although no high-level evidence is available, there appeared to be significant reductions in mortality and morbidity when HBOT was used as an adjunct to standard care for gas gangrene.</td>
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</table>
4.5.2 Surgical site infection

One prospective non-randomised controlled trial was identified relating to surgical site infection (SSI) as shown in Table 4.5-2. Of 32 patients developing postoperative organ/space sternal SSI following cardiac surgery, 14 received HBOT in addition to standard care, while those who refused HBOT or had contraindications received standard care. No statistically significant differences were observed in duration of infection or time from diagnosis to wound closure between those in the HBOT group versus the control group. However, the infection relapse rate (p=0.024), duration of intravenous antibiotic use (p=0.036) and total hospital length of stay (p=0.026) were significantly lower in the HBOT group. These findings were considered promising, however inadequate methodological description makes it difficult to judge their robustness and the confidence that can be placed on them. The results require confirmation in a larger study population with randomisation between groups.
Table 4.5-2  Evidence on using HBOT to treat surgical site infection - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barili et al., 2007&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Non-randomised controlled trial</td>
<td>To evaluate the effect of HBOT on organ/space sternal SSI following cardiac surgery that required sternotomy.</td>
<td>14 patients received HBOT. The control group of 18 patients comprised those unsuitable or not consenting to HBOT. Baseline characteristics were similar between groups, except for a higher prevalence of peripheral vascular disease in the HBOT group. The HBOT group received one HBOT session per day for 90 minutes until the wound was sterilised. The mean number of sessions was 17.1±5.8. All patients received standard wound care. Outcomes measured were: duration of infection, infection relapse rate, hospital readmission rate, duration of antibiotic use and total length of hospital stay.</td>
<td>Patients who developed organ/space SSI following cardiac surgery. Diagnosis based upon Centers for Disease Control and Prevention criteria.</td>
<td>Duration of infection and time from diagnosis to wound closure did not differ significantly between groups. Infection relapse was less likely in the HBOT group HBOT=0 of 14; control=6 of 18 (p=0.024). Duration of intravenous antibiotic use was lower in the HBOT group HBOT=47.8±7.4 days; control=67.6±25.1 days (p=0.036). Total hospital stay was lower in the HBOT group HBOT=52.6±9.1 days; control=73.6±24.5 days (p=0.026).</td>
<td>HBOT as an adjunct to standard care represents a valuable tool in treating postoperative organ/space sternal SSI.</td>
</tr>
</tbody>
</table>
4.5.3 Livedoid vasculopathy

A small uncontrolled study (Table 4.5-3) concluded that HBOT was a relatively safe, rapid and effective treatment for patients with livedoid vasculopathy. The authors acknowledged that an RCT was needed to verify the findings.
### Table 4.5-3  Evidence on using HBOT to treat livedoid vasculopathy - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juan et al, 2006</td>
<td>Uncontrolled</td>
<td>To analyse the long-term effects and safety of HBOT in patients with</td>
<td>12 adults (18–37 years) with livedoid vasculopathy. HBOT: 100% O$_2$, 2.5 ATA, 60 min, 5 days a week for 2–5 weeks. No control group. Outcomes: healing, recurrence, analgesic use, side effects. Average follow up was 20.8 months. Confirmed idiopathic livedoid vasculopathy.</td>
<td>Exclusion criteria: history of chest or ear surgery, seizure, malignancy or pregnancy.</td>
<td>4 patients withdrew (2 because of exacerbated leg pain after the first session, 1 following syncope in the chamber and 1 for personal reasons). In 8 patients leg ulcers healed within 2–5 weeks, 6 relapsed but responded to additional HBOT. No significant side effects were seen (1 suffered ear pain and 2 others exacerbation of leg pain).</td>
<td>HBOT is a relatively safe, fast and effective treatment for livedoid vasculopathy.</td>
</tr>
</tbody>
</table>
4.6 Acute coronary syndrome

Introduction

Acute coronary syndrome (ACS) is the term used to describe diseases of the cardiovascular system that are associated with possible or actual death of heart tissue, resulting from impaired blood supply. ACS is generally caused by thrombus formation on an atherosclerotic plaque in one or more vessels. The thrombus reduces the blood supply to heart tissue, potentially causing myocardial infarction (MI) and death. Optimal patient management depends on the risk of MI, but usually includes treatment with aspirin, nitrates, β-blockers, low molecular weight heparin and statins with or without glycoprotein IIb/IIIa inhibitors.

HBOT has been proposed as adjunctive treatment, following uncontrolled human studies and use in an animal model. It is proposed that exposure to oxygen under pressure reverses hypoxia in areas of heart tissue that are marginally perfused and promotes tissue repair.

Evidence identified

Two HTA reports, one systematic review and one RCT published as two articles were identified which met the inclusion criteria for this review. The studies informing on the use of HBOT to treat ACS are described in Table 4.6-1.

Evidence quality

The MSAC HTA report and the Cochrane review used comprehensive search strategies; the Cochrane review sought published and unpublished studies in any language, whereas the MSAC review was restricted to studies in English. The AETMIS review was limited to studies published in English and French and identified only one trial. This trial and another were identified by the MSAC and Cochrane reviews, and therefore further description is based on the Cochrane review.

Four trials, published from 1973–2004, were reported in the Cochrane review. The trials were generally of low quality with just one trial describing randomisation procedures and the other giving details of allocation concealment. Only one trial used sham therapy and described blinding of outcome assessment. However, this trial comprised a heterogeneous group of patients and only reported on short-term outcomes.

The literature search conducted for this report identified a further two papers relating to a recent clinical trial.

These reported on a small trial of 74 patients and gave no details of randomisation procedures or allocation of concealment. In addition, the trial did not use sham therapy and only considered short-term outcomes. The quality of this trial was, therefore, described as low.

Results

The Cochrane review considered a total of 462 patients randomised to either standard care or standard care with one or more sessions of HBOT. Three trials included patients with confirmed MI and the fourth ACS patients. The primary outcomes of interest were death and major adverse coronary events (MACE). Three trials reported on death as an outcome, and pooling of results showed no statistically significant reduction in the risk of death following HBOT. The results from the one trial showed a statistically significant reduction in the risk of MACE following HBOT. However, the findings were sensitive to the effects of patients withdrawing from the studies. A number of secondary outcomes were also reported, most by only one trial. There was a statistically significant reduction in risk of dysrythmia in the HBOT group in one trial but this result was sensitive to the effect of patient withdrawal. One trial showed a statistically significant reduction in time to pain relief in patients receiving HBOT.

The recent trial reported improved outcomes for the HBOT group in terms of peak creatine phosphokinase levels, and wall motion score index and ventricular volumes (both measures of ventricular function). Although statistically significant differences were observed, the trial was small and of poor quality and confidence intervals surrounding the outcome measures were wide. These results were, therefore, considered with caution.

Discussion

Current guidelines for the management of ACS indicate immediate percutaneous coronary intervention and the practicabilities of providing adjunctive HBOT would be very challenging. The Cochrane review concluded that RCT evidence on the clinical effectiveness of adjunctive HBOT for ACS does not justify its routine application. The more recent RCT did not provide evidence to modify this conclusion. Although all trials showed a trend toward improved outcome in the HBOT group, using a number of the assessment measures, the clinical significance of these surrogate outcomes is unclear. The component trials were also small, and suffered from poor reporting and methodological shortcomings. Therefore there is not currently evidence to support the use of HBOT in patients with ACS.
Bennett et al., 2005

**Systematic review**

To assess the benefit and harm of adjunctive HBOT when treating ACS.

A comprehensive search of electronic databases, reference list scanning, expert opinion and hand searching. Search conducted in Nov 2004. Quality assessment was in line with the Cochrane Handbook. Meta-analysis used a fixed-effects model as there was no evidence of heterogeneity.

Participants were adults with ACS with or without ST-segment elevation. Study design: RCTs comparing the effect of treatment for ACS (including thrombolysis), considered HBOT versus a no HBOT comparator. Intervention: HBOT at pressures of 1.5–3.0 ATA on one or more occasion. Primary outcomes were death and rate of MACE. 11 secondary outcomes were also considered.

4 trials, published from 1973–2004 included 462 participants. 3 trials of patients with confirmed MI and 1 of ACS patients. The trials were considered of low quality.

Death (3 trials): HBOT RR 0.64 (95% CI: 0.38, 1.06; p=0.08). The outcome was sensitive to patient withdrawal (best case RR 0.42; 95% CI: 0.26, 0.70; p=0.0008 and worst case RR 1.41; 95% CI: 0.91, 2.18; p=0.12).

MACE at 8 months (1 trial, 61 patients): HBOT RR 0.12; 95% CI: 0.02, 0.85; p=0.03). The outcome was sensitive to patient withdrawal (best case RR 0.09; 95% CI: 0.01, 0.61; p=0.22 and worst case RR 0.56; 95% CI: 0.23, 1.40; p=0.22).

Secondary outcomes:
- One trial found that patients receiving HBOT were significantly less likely to suffer dysrythmia (25 of 103 versus 43 of 105) though the findings were sensitive to withdrawals.
- One trial found that the mean time to pain relief was statistically significantly lower in the HBOT group (261 mins versus 614 mins).
- One trial found no statistically significant difference in creatine phosphokinase levels post-treatment.
- Two trials reported on improved left ventricular function, but pooling was not appropriate. Neither trial showed a statistically significant difference between groups.
- One trial reported on length of hospital stay and did not show a statistically significant difference between groups.
- Adverse effects: two trials reported the incidence of tympanic membrane rupture due to barotrauma. 1 subject of 127 suffered tympanic membrane rupture (not statistically significant). Three trials reported no neurological oxygen toxicity.

Limited evidence showed that HBOT reduces the incidence of MACE, complete heart block and the time to relief from angina. There was a trend toward favourable outcomes for mortality, length of hospital stay and left ventricular function with HBOT. The small number of trials, patients included and the low methodological quality of the studies led the authors to conclude that routine adjunctive use of HBOT for ACS patients is not justified. The authors suggested that the positive outcomes observed indicated that RCTs should be conducted to prove definitive evidence on efficacy.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Services Advisory</td>
<td>Technology</td>
<td>To evaluate the efficacy of HBOT in acute MI, cerebrovascular disease and peripheral obstructive arterial disease.</td>
<td>MEDLINE, HealthSTAR, EMBASE, Cochrane library, CINAHL, Nursing collection, biological abstracts, best evidence, HTA group websites, DORCTHIM, secondary references, books, hand searching and expert opinion. Quality assessed for internal and external validity and classified according to the NHMRC revised evidence hierarchy.</td>
<td>Articles were excluded if they did not assess a pre-agreed condition, were uncontrolled, did not have a comparator group or were not published in English. There was no attempt to pool outcomes.</td>
<td>Identified two trials included in Bennett, 2005 (see above).</td>
<td>There was no firm evidence to recommend HBOT for acute MI, though improved pain relief justifies further studies.</td>
</tr>
<tr>
<td>Advisor Committee, 2001**</td>
<td>assessment report</td>
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<tr>
<td>Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé, 2001**</td>
<td>HTA</td>
<td>To review the efficacy of HBOT in the treatment of a number of conditions.</td>
<td>Limited electronic database search and bibliography scanning. Covered the literature to July 1999.</td>
<td>Studies in English or French.</td>
<td>The one trial identified was included in Bennett, 2005 (see above).</td>
<td>Promoting the use of HBOT to treat myocardial ischaemia is not justified.</td>
</tr>
<tr>
<td>Dekleva et al., 2004**, Vlahovic et al., 2004**</td>
<td>RCT</td>
<td>To assess the benefit of thrombolysis in combination with HBOT on left ventricular function.</td>
<td>RCT of 74 consecutive MI patients meeting the study criteria. <strong>Intervention:</strong> Thrombolytic therapy with HBOT at 2 ATA for 60 mins at mean of 13h post-symptom onset versus thrombolytic therapy alone.</td>
<td>Age ≤70 years, chest pain lasting &gt;30 mins ST-segment elevation of ≥2mm in at least 2 contiguous ECGs, transient creatine phosphokinase and/or MB isoenzyme elevation. First ECG within 24h of pain onset, no signs of severe heart failure, no malignant arrhythmia.</td>
<td>A statistically significant reduction in peak creatine phosphokinase was observed in the HBOT group (p=0.018). The Wall motion score index was lower in the HBOT group (p=0.002). Statistically significant differences were observed in measures of ventricular volume although the confidence intervals were very wide. No adverse events were observed during HBOT.</td>
<td>Although the trial identified differences in some outcome measures, the confidence intervals (not always reported) were wide and the clinical significance of the findings were unclear. The method of randomisation was not reported and allocation concealment was unclear.</td>
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</table>
4.7 Stroke

Damage to brain tissue resulting from impaired blood flow (ischaemic stroke) or bleeding within the brain (haemorrhagic stroke) are major causes of morbidity and mortality worldwide. Hypoxia occurs in brain tissue following an ischaemic event, and adjunctive HBOT has been proposed to improve oxygen delivery to the affected tissue and reduce cerebral oedema. Furthermore, it has been suggested that HBOT may protect areas of the brain that are marginally viable. However the brain may be at particular risk of oxygen toxicity, and HBOT in stroke patients has the potential to be harmful rather than beneficial.

Evidence identified

The AHRQ report identified three technology assessments and a Cochrane review, which considered the effectiveness of HBOT in the treatment of stroke. In addition, the literature search identified a further systematic review and a pilot clinical trial. The studies informing on the use of HBOT to treat stroke are described in Table 4.7-1.

Evidence quality

The MSAC report was a well conducted review of HBOT for a number of indications including cerebrovascular disease. The authors identified two RCTs and a case series. The AHRQ report, also reported in Carson et al., was a well-conducted review of HBOT for brain injury, cerebral palsy and stroke. In this report, five controlled trials were identified of which four were randomised and one was reported in two publications and one was not randomised. No attempt was made to conduct a quantitative synthesis of the findings as few common outcome measures were reported.

The British Columbia report was based on a limited literature search on HBOT for brain injury and stroke, which identified only two of the previously mentioned trials.

One study was identified that had not been included in a previous review. This trial of adjunctive hyperbaric treatment for acute embolic stroke did not describe randomisation procedures or allocation concealment. The baseline characteristics of the control and treatment groups were comparable, however there was no indication of any attempt to blind patients or outcome assessors to group allocation. Statistical analysis was on an intention-to-treat basis.

Results

The MSAC HTA reported that both component RCTs described randomisation methods poorly and that outcome measures differed and could not be pooled. The results were, therefore, presented in narrative form. The authors reported conflicting evidence on the effectiveness of the intervention and concluded that 'no firm and generalisable' evidence was available to support the use of HBOT in stroke.

The AETMIS study concluded that, although there was no evidence of effectiveness for HBOT in the treatment of cerebral ischemia, the area warrants further research.

In the AHRQ report both controlled and uncontrolled studies were considered. The authors concluded that the high-quality trials identified did not provide evidence for effectiveness of any given dose or frequency of HBOT. Many observational studies reported good or very good results, however flaws in study design meant that these could not be attributed to HBOT. Overall, the authors were unable to draw conclusions regarding the effectiveness of HBOT.

The Cochrane review identified three RCTs with a total of 106 patients and presented pooled mortality data. No significant differences were observed in mortality at 6 months. The authors concluded that, although there was no evidence of effectiveness of HBOT for this indication, there are insufficient clinical trials to provide clear guidance.

Only one small pilot RCT study was found that had not been included in the review articles. Imai et al. assessed the safety and efficacy of HBOT combined with intravenous edaravone, in the management of acute embolic stroke in the anterior cerebral circulation. The study reported a favourable outcome in 6 of 19 patients for HBOT with edaravone (scores 0–1 on the modified Rankin scale at 90 days) compared with 1 patient of 19 in the control group. Improvement in National Institute of Health Stroke Scale (NIHSS) score was also significantly better in the HBOT group. The authors concluded that HBOT combined with intravenous edaravone was effective in patients with acute embolic stroke. However this study was judged of poor quality, as the methods of randomisation were not clear and there was no indication of allocation concealment or blinding.

Discussion

This report identified a number of reviews of the use of HBOT as an intervention for stroke, but they were based on a small number of variable quality RCTs. The component trials also varied in terms of the patient population considered, outcome measures and the hyperbaric schedules used. In addition, review quality varied both in terms of the literature identified and the synthesis and interpretation of the original trial results. For example, the Cochrane review presented pooled results from three trials reporting mortality 3–6 months postintervention; however other reviews indicated that an absence of common outcomes prevented data pooling. The results of the Nighoghossian trial were also subject to variable interpretation, with authors placing emphasis on different elements of the analysis.

The overall conclusions of the reviews were, however, similar as they all noted no evidence of effectiveness for...
4.7 Stroke

HBOT in stroke. Each review also indicated that improved design and reporting of future clinical trials is required to establish a role for HBOT in this condition. The most recently published trial was not included in the reviews. It presented more positive data but was small and of poor quality, and was not sufficient basis to recommend a change in the conclusions of previous systematic reviews.

The evidence would therefore not support the routine use of HBOT in the treatment of stroke.
### Table 4.7-1 Evidence on using HBOT to treat stroke - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
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<tbody>
<tr>
<td>Medical Services Advisory Committee, 2001</td>
<td>Technology assessment report</td>
<td>To evaluate the safety and effectiveness of HBOT in patients with stroke.</td>
<td>MEDLINE, HealthSTAR, EMBASE, Cochrane library, CINAHL, Nursing collection, biological abstracts, best evidence, HTA group websites, DORCTHIM, secondary references, books, hand searching and expert opinion. Quality assessed for internal and external validity and classified according to the NHMRC revised hierarchy of evidence.</td>
<td>Articles were excluded if they did not consider a pre-agreed condition, were uncontrolled, did not have a comparator group or were not published in English.</td>
<td>2 RCTs were identified. The studies were of moderate quality although randomisation methods were unclear and only 1 study described use of double-masked procedures. It was not possible to pool study data, as different patient outcomes were considered. 1 trial reported statistically significant differences between intervention and control groups at 1 year, based on 2 of 3 outcome measures. The second trial showed that the neurological examination score for the control group improved by 15.9±3.2 points (p&lt;0.0003), while the intervention group improved by 12.2±4.8 (p&lt;0.03). As better improvement was seen in the control group the study was stopped for ethical reasons.</td>
<td>Both studies examined a few clinical outcomes. The evidence base was contradictory and HBOT was not recommended for stroke patients. Nighoghossian noted no statistically significant difference when pre- and post-therapy differences were compared between intervention and control groups.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/characteristics</td>
<td>Inclusion/exclusion criteria</td>
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<td>Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé, 2001&lt;sup&gt;10&lt;/sup&gt;</td>
<td>HTA</td>
<td>To review the efficacy of HBOT in the treatment of a number of conditions.</td>
<td>Limited electronic database search and bibliography scanning. Literature in databases was searched to July 1999.</td>
<td>Studies in English or French.</td>
<td>Identified 1 RCT and 1 case series. The RCT showed no significant difference in outcomes between treatment and control groups. The case series recommended use of HBOT but the study was subject to selection bias and the severity of injuries was not clearly indicated.</td>
<td>There was no evidence of a beneficial effect for HBOT in cerebral ischaemia but the area warrants further research.</td>
</tr>
<tr>
<td>McDonagh et al., 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>HTA</td>
<td>To establish benefit and harm of using HBOT to treat brain injury, cerebral palsy and stroke.</td>
<td>MEDLINE, Cochrane library, HealthSTAR, EMBASE, CCTR, CDSR, DARE, CINAHL, MANTIS, AltHealthWatch, bibliographic databases from professional bodies and HBOT practitioners, secondary references and hand searching. Quality was assessed for internal and external validity and an overall quality rating was given (good, fair, or poor) according to USA preventive services task force methods. Meta-analysis used a fixed-effects model to consider mortality outcome.</td>
<td>Controlled clinical trials and observational studies in English were included. Case series and reports in languages other than English were excluded.</td>
<td>Controlled clinical trials 4 RCTs and 1 controlled clinical trial were reviewed. 3 RCTs were considered of fair quality, 1 was of poor quality due to the lack of reporting randomisation or allocation concealment procedures. Few outcomes were common to the studies and no attempt was made to pool data. 3 RCTs found no difference in neurological measures, but 1 RCT and the non-randomised comparative trial (both were considered of poor quality) reported that HBOT improved neurological outcome for some measures. Observational studies 17 studies of poor quality were included. Most reported favorable results but failed to show that the benefits could be attributed to HBOT.</td>
<td>There was insufficient evidence to determine the effectiveness of HBOT in stroke patients. It was noted that improvements in the design and reporting of future clinical trials in this area are required. Measurement should consider outcomes of importance to patients and caregivers.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
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<td>Alternative therapy evaluation committee for the insurance corporation of British Columbia, 2003[1]</td>
<td>Systematic review</td>
<td>To review evidence supporting the use of HBOT for traumatic brain injury.</td>
<td>MEDLINE, HealthSTAR EMBASE and expert opinion.</td>
<td>Controlled clinical trials of HBOT to treat brain injury and titles suggesting clinical trials. English language reports, published in peer reviewed journals.</td>
<td>6 studies with control groups and reporting clinical outcomes were reviewed. 2 studies presented evidence on the use of HBOT in stroke. Results from individual studies were not given and no quantitative synthesis was undertaken.</td>
<td>The studies provided moderately strong evidence against the use of HBOT for treatment of stroke.</td>
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<tr>
<td>Imai et al., 2006[2]</td>
<td>Small pilot RCT</td>
<td>To test the safety and efficacy of HBOT with IV edaravone for treatment of acute embolic stroke.</td>
<td>Participants: presentation within 48h of stroke onset. 38 patients randomised (HBOT + edaravone 19; control 19). HBOT – 1h/day for 7 days combined with 30mg IV edaravone over 60 min before and after each HBOT session. Both groups were given 10000U IV heparin/day for 7 days. Outcomes: Modified Rankin scale score at 90 days (favorable outcome), NIHSS scores at 7 days, survival for 90 days, complications and abnormal findings. Analysis based on intention to treat.</td>
<td>Matched baseline characteristics Exclusion criteria: Patients with no neuroimaging evidence of complete ischaemic stroke (37), fibrinolytic treatment (13), baseline NIHSS score of 4 or less (12), medical contraindication for HBOT (5), rapid improvement of neurological signs (4), seizure at stroke onset (2) and refusal to participate (1).</td>
<td>6 of 19 patients in the HBOT group and 1 of 19 in control group had favorable outcomes (scores 0-1 on modified Rankin scale) at 90 days (p&lt;0.05). NIHSS scores at 7 days did not differ significantly between groups, intragroup improvement of NIHSS scores was significantly better for the HBOT group. No significant difference in the number of patients surviving at 90 days. No serious complications or abnormal findings found in either group.</td>
<td>HBOT therapy combined with IV edaravone is effective for the treatment of patients with acute embolic stroke in the anterior cerebral circulation. The method of randomisation was unclear, there was no indication of allocation concealment or blinding to group assignment. The trial was considered of poor quality.</td>
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<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/characteristics</td>
<td>Inclusion/exclusion criteria</td>
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<td>Bennett et al., 2005&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Systematic review (Cochrane)</td>
<td>To evaluate the effectiveness and safety of adjunctive HBOT in the treatment of acute ischaemic stroke.</td>
<td>MEDLINE, Cochrane Stroke Group Trials Registry, CENTRAL, DORCTHIM, EMBASE, CINAHL, secondary references, hand searching and expert opinion. Quality assessed for internal validity using an adaptation of the method of Schulz, 1995. Meta-analysis using a fixed-effects model for mortality.</td>
<td>RCTs comparing the effect of adjunctive HBOT with control (no treatment or sham). No language restrictions. Patients of any age or sex with acute ischaemic stroke. Exclusion criteria: Clinical trials not meeting the above criteria. Intervention: standard therapy versus HBOT or intensive combination therapy. HBOT administered in a compression chamber at 1.5–3.0 ATA for 30–120 min at least once daily. Outcomes: Mortality rate (death), severe functional disability, function and adverse events.</td>
<td>The review included 3 RCTs. No statistically significant differences in mortality rate were observed at 6 months (RR=0.61; 95% CI: 0.17, 2.2; p=0.45). Of the 15 scaled disability measures and functional scores only two scales indicated improvement following HBOT. At 1 year follow up the Trouillas Disability Scale was lower (mean difference 2.2; 95% CI: 0.15, 4.3) and the Orgogozo Scale score was higher (mean difference 27.9; 95% CI: 4.0, 51.8).</td>
<td>Evidence from 3 small RCTs was insufficient to suggest that HBOT improved clinical outcome after acute ischaemic stroke. Evidence is insufficient to provide guidance and clinical benefit seems unlikely.</td>
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4.8 Traumatic brain injury

Introduction

Head injury occurs with an incidence of approximately 150,000 cases per year in the UK, and is associated with significant levels of disability. The theoretical mode of action of HBOT in the treatment of traumatic brain injury (TBI) is similar to that suggested for the treatment of stroke (Section 4.7). With head injury there is also a theoretical possibility of HBOT causing oxygen toxicity, and resulting in harm rather than benefit.

Evidence identified

A Cochrane systematic review of four randomised or quasi-randomised trials assessed the use of adjunctive HBOT for TBI. The trials compared adjunctive HBOT with standard intensive treatment regimens. An ECRI systematic review was completed after the date of the Cochrane review and included the same three randomised controlled trials but not the quasi-randomised study. Given this overlap and the broader coverage of the Cochrane review, the ECRI review was not considered further. Two RCTs in the Cochrane review were included in another systematic review with five observational studies. The latter review formed part of a larger AHRQ technology report published in 2003. The trials included in these reviews were published from 1974–2001 and the observational studies from 1969–2001. The studies informing on the use of HBOT to treat TBI are described in Table 4.8-1.

Evidence quality

Both systematic reviews used comprehensive search strategies; the Cochrane review sought published and unpublished studies in any language, whereas the AHRQ review restricted inclusion to studies published in English. The last search dates were April 2006 and December 2003, respectively. Both reviews used explicit inclusion criteria and systematically assessed study quality. Of the identified trials, allocation concealment was inadequate in one (quasi-randomised) trial and was unclear in the other three; none described randomisation procedures.

Neurologists assessing long-term outcomes in one trial were blinded to treatment allocation.

The quality of the RCTs common to both reviews was assessed, using different criteria, as low by the Cochrane review (all component trials were designated as low quality) and fair by the AHRQ. As randomisation and allocation concealment were not described in either trial the low quality rating is more appropriate and in line with the SIGN appraisal advice.

Results

The four trials reported in the Cochrane review included a total of 382 participants. The oxygen dose per session and in total varied between trials, the lowest dose was 1.5 ATA for 60 minutes per day and the highest 2.5 ATA for 40–60 minutes 10 times over 4 days. The number of sessions ranged from 10.5–40. Follow up ranged from 12 days after admission to 1.5 years.

The primary outcomes of interest to the Cochrane review were good functional outcome (defined as Glasgow Outcome Score 1 or 2, described as ‘fully recovered’ or ‘returning to normal activities of daily living’) and survival. The secondary outcomes were activities of daily living (ADL), intracranial pressure (ICP) and adverse events.

Meta-analysis of two trials (159 participants) showed no significant difference in the proportion of patients with good functional outcome at 4 weeks. One trial (55 participants) reported data at 6 months follow up and showed significant benefit in the HBOT group (RR 2.8; 95% CI: 1.4, 5.5; p=0.004). Another (168 participants) reported follow up at 12 months, with no significant difference between adjunctive HBOT and standard treatment.

Meta-analysis of follow-up data from three trials (325 participants) showed a significantly reduction in the risk of death in favour of HBOT (RR 1.46; 95% CI: 1.13, 1.87; p=0.003). There was no evidence of statistical heterogeneity between the trials, despite final follow up being 12 months in two trials and 12 days in the other. Sensitivity analysis showed that loss to follow up did not affect the findings.

None of the included trials reported on ADL. Data from one RCT assessed ICP but interpretation was limited by the introduction of prophylactic myringotomy in the HBOT group during the study, as the investigators noted higher than expected ICP in HBOT treated patients. Post-hoc subgroup analysis showed that mean peak ICP was significantly lower in patients who received HBOT and myringotomy (n=42) (WMD 8.2; 95% CI: 1.72, 14.68; p=0.01) but not when comparing patients who received only HBOT (n=37) versus the control group (n=77).

None of the trials reported any adverse effects in the control groups. Meta-analysis showed a significantly increased risk of serious pulmonary complications in patients treated with HBOT as reported in two RCTs (RR 0.06; 95% CI 0.01, 0.47; p=0.007). Overall, 15 of 115 HBOT patients were affected, compared with 0 of 113 in the control group. In some cases pulmonary complications led to withdrawal of HBOT. In one trial 2 of 84 patients in the HBOT group suffered an isolated generalised seizure, indicative of neurological oxygen toxicity, and two experienced middle ear barotrauma (haemotympanum).

Five observational studies failed to provide better evidence on effectiveness or adverse effects.

Discussion

Two well-conducted systematic reviews identified some evidence that adjunctive HBOT may reduce the risk of death from TBI, but there was little evidence of better functional outcome among survivors. Adverse effects were poorly assessed by the studies included in the reviews.
Cautious interpretation of the findings is warranted because of methodological limitations and inadequate reporting in the component studies\textsuperscript{103,105}.

ECRI\textsuperscript{104} identified an ongoing RCT to examine the effects of early HBOT on TBI which aims to recruit 80 patients. The study is due to complete in November 2008 and, if adequately performed, should add to the current limited evidence base, however at present there is insufficient evidence to support the routine use of HBOT in the treatment of TBI.
### Table 4.8-1  Evidence on using HBOT to treat traumatic brain injury - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
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<tr>
<td>ECRI, 2006</td>
<td>Systematic review</td>
<td>To assess whether adding HBOT to standard TBI treatment decreases the severity of complications and improves cognitive function. To assess adverse events related to HBOT.</td>
<td>Systematic search undertaken (details not reported).</td>
<td>Full articles on patients with acute TBI, with a control group and at least 10 patients in each study arm. Articles in English only.</td>
<td>3 RCTs (Ren, 2001; Rockswold, 1992; Artu, 1975).</td>
<td>The small number of patients studied and the inconsistent outcome measures reported make it impossible to determine the effect of HBOT on cognitive function and survival. Serious side effects were rare, but the technology is not entirely risk free. Bennett et al., 2004.</td>
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<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/characteristics</td>
<td>Inclusion/exclusion criteria</td>
<td>Results</td>
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<tr>
<td>Bennett et al., 2004</td>
<td>Cochrane systematic review</td>
<td>To assess the benefits and harm of adjunctive HBOT for TBI.</td>
<td>MEDLINE, EMBASE, CINAHL, CENTRAL, DORCTHIM, hand searching of hyperbaric journals and proceedings and expert opinion.</td>
<td>RCTs or quasi-randomised trials in patients admitted to intensive care or intensive neurosurgical facility with acute TBI following blunt injury, comparing HBOT (compression chamber at 1.5–3.5 ATA for 30–120 mins at least once) with standard treatment, and reporting at least one outcome of interest. There were no language restrictions.</td>
<td>3 RCTs (Ren, 2001; Rockswald, 1992; Artru, 1976) and 1 quasi-randomised trial (Holbach, 1974) including 382 participants. No study described randomisation procedure. Carers were not blinded in any study, 1 study blinded outcome assessors. No significant difference in the proportion of patients with good functional outcome at 4 weeks (2 trials, 159 participants). 1 trial (n=55) reported significant benefit in the HBOT group at 6 months (RR 2.8; 95% CI: 1.4, 5.5; p=0.004), 1 trial (n=168) found no significant difference at 12 months. Meta-analysis of final follow-up data (3 trials, 325 participants) showed a significant reduction in the risk of death in favour of HBOT (RR 1.46; 95% CI: 1.13, 1.87; p=0.003). Meta-analysis of 2 RCTs showed significantly increased risk of serious pulmonary complications with HBOT (RR 0.06; 95% CI: 0.01, 0.47; p=0.007).</td>
<td>Adjunctive HBOT significantly reduced the risk of death in patients with TBI but there was little evidence that HBOT is associated with a good outcome.</td>
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**Study**  
McDonagh et al., 2004

<table>
<thead>
<tr>
<th><strong>Type</strong></th>
<th>Systematic review</th>
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<tr>
<td><strong>Aim</strong></td>
<td>To identify the benefits and harm of HBOT in TBI</td>
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<tr>
<td><strong>Search strategy/characteristics</strong></td>
<td>MEDLINE, EMBASE, CINAHL, the Cochrane Library, DARE, NNTapot RCTs, ACP-JNC, PIN, MANTIS, UHMS, DORCTHIM, EUBS, International Congress on Hyperbaric Medicine and National Baromedical Services Inc. libraries, reference lists, textbooks, and expert opinion</td>
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<tr>
<td><strong>Inclusion/exclusion criteria</strong></td>
<td>Studies of patients with TBI given HBOT by any protocol, reporting health outcomes (including mortality and functional status) and published in English. Before-and-after studies and time series were included if they had &gt;10 patients. Studies reporting only intermediate outcomes (other than ICP) were excluded, as were case reports.</td>
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</table>

### Results

2 RCTs (Rockwald, 1992; Artru, 1976) including 228 participants and 5 observational studies (Ren, 2001; Rockswald, 2001; Suckoff, 1982; Hayakawa, 1971; Mogami, 1969) were included. Most observational studies had no control group and outcome assessors were not blinded. One RCT showed no significant difference in mortality (48% versus 55%) or morbidity at 1 year. The other showed a significant decrease in mortality with HBOT (17% versus 30%; p=0.037). 2 observational studies indicated potential for early reduction in ICP in some patients but rebound elevations, to levels higher than those pretreatment, were also seen. Adverse effects were not assessed.

### Conclusions and comments

There was insufficient evidence to confirm the cost-effectiveness of HBOT for TBI. There may be a small mortality benefit in subgroups of patients. Effects on functional status and adverse effects were not evaluated.
4.9 Soft-tissue radiation injury

Introduction

Soft-tissue radiation injury (STRI) is a late complication of radiation therapy for the treatment of cancer. Following irradiation, tissues undergo a progressive deterioration characterised by a reduction in the density of small blood vessels and the replacement of normal tissue cells with dense fibrous tissue. If this process continues until there is insufficient oxygen supplied to sustain normal function, an overt injury will result. This situation is frequently exacerbated by secondary damage due to infection or surgery in the affected area. This progressive and delayed radiation damage may reach a critical point where the tissue breaks down to form an ulcer or area of cell death (radiation necrosis, or radionecrosis)\(^{106}\). STRI can affect any organ system, although some tissues are more sensitive to radiation effects than others. In this review, late radiation effects on bone are treated separately because of historical precedent, and the fact that treatment is frequently administered to prevent necrosis of bone following surgery in an irradiated area.

Evidence identified

Literature search identified three HTAs\(^{10,63,107}\) and eight systematic reviews\(^{108-115}\) on the use of HBOT in STRI that met the inclusion criteria. One additional controlled trial\(^{116}\), published after the last systematic review, was also identified. In addition, one of the trials\(^{117}\) included by Bennett et al.\(^{108}\) was only available as a meeting abstract at the time of this review, but has recently been published in full so was considered separately. Numerous case series studies were also retrieved but these were not included as they did not add to the evidence base. Details of included studies are presented in Table 4.9.1.

The included studies considered the use of HBOT both as a prophylactic treatment before surgery, to prevent STRI, and to treat pre-existing STRI. The areas of the body assessed in these studies were numerous and included: the larynx (laryngeal chondonecrosis), the head and neck, the rectum (proctitis), the bladder (cystitis), the breast and larynx (laryngeal chondonecrosis), the head and neck, the chest wall, the nervous system (myelitis, optic neuropathy, brain necrosis, brachial plexopathy) and the extremities.

Evidence quality

The HTAs and systematic reviews were all considered to be of acceptable quality, but some were more controlled than others. The Cochrane reviews\(^{108,110,112,113}\) met most of the assessment criteria. Other systematic reviews and HTAs failed to report on inclusion/exclusion criteria\(^{114}\), details of the literature search methodology and the methodology used for quality assessment of the evidence\(^{107,115}\).

Despite variability in the rigour with which the secondary studies were carried out, they all appeared to identify the same small number of primary studies. The main quality issues related to the conduct of the primary source studies rather than the methodology of the secondary studies. The authors of the secondary studies concluded that primary studies were of poor methodological quality with considerable variability in patient inclusion criteria, treatment protocols, measurement and reporting of outcomes.

Results

The Bennett et al.\(^{108}\) Cochrane review identified four RCTs studying the effects of HBOT on late radiation tissue injury (several of which were also included in some earlier reviews. The other HTAs and reviews did not report on additional RCTs, so Bennet et al.\(^{108}\) was considered to provide the strongest evidence base for this indication and will be discussed here. The included RCTs considered the use of HBOT to treat STRI affecting various anatomical sites. Given variations in the tissue sites involved, methodological quality, outcomes assessed and baseline characteristics, the study results were not pooled in the Cochrane review but were reported separately.

Although an RCT by Clarke et al.\(^{117}\) was included within the systematic review, the study had not yet been published and therefore the recent publication of the full study was appraised in addition to the Bennett et al. review\(^{108}\). This double-blind crossover study examined 150 patients with problematic radiation proctitis, half of whom received HBOT, at 2.0 ATA for 90 minutes, once daily, five times per week; the other half received sham HBOT. Patients who received HBOT had a significantly greater likelihood of healing or improvement of proctitis after initial allocation OR=5.93 (95% CI 2.04 to 17.24) (RR=2.67; 95% CI: 1.19, 5.99; p=0.02). An improvement in mean SOMA-LENT (late effects normal tissue-subjective, objective, management, analytic) of 5.00 in the HBOT group versus 2.61 in the sham HBOT group (p=0.0019) was also observed.

Hulshof et al.\(^{118}\) randomised 7 patients with cognitive disorders following brain irradiation to receive either immediate or delayed treatment (after 3 months) of 30 HBOT sessions over 6 weeks. Small improvements were noted in some neuropsychological parameters for some patients following HBOT, but no statistically significant difference in test performance was seen at either 3 or 6 months.

The use of HBOT to treat patients with established radiation-related brachial plexopathy was assessed in a double-blind study by Pritchard et al.\(^{119}\). Thirty-four patients received either 30 HBOT sessions or sham HBOT. No statistically significant difference between groups was seen in the primary outcome of warm sensory threshold at either 1 week or 1 year after treatment. Similarly, there was no statistically significant difference between groups in the resolution of swelling or in quality of life, as measured by SF-36 scores, 12 months after treatment. In the report by Marx\(^{120}\), 160 patients who required major soft-tissue surgery or flaps in a previously irradiated area, were randomised to receive either HBOT for 20 preoperative and 10 postoperative sessions or to control treatment (not specified). Few details of the trial are available but the Cochrane review noted that there was a statistically significant higher likelihood of wound...
dehiscence in the control group compared with patients in the HBOT group (RR=8.67; 95% CI: 2.73, 27.49; p=0.0002).

A recent case-controlled study\textsuperscript{116} considered the use of HBOT to prevent radiation-induced brain injury (radiation necrosis and white matter injury), in patients with brain metastases treated with stereotactic radiosurgery (SRS). Data were available for 78 patients, 32 of whom received HBOT. Logistic regression showed no statistically significant association of HBOT with radiation necrosis or white matter injury, but survival analysis demonstrated that non-use of HBOT was a predictor of brain injury at 1 year after surgery (p=0.02).

Most studies included in the secondary literature comprise case series and case studies, and generally reported improvements in outcome following HBOT therapy. In the absence of a control group however little weight can be attached to these results.

None of the controlled studies reported data on adverse events.

Discussion

The Clarke et al. trial\textsuperscript{117} was well conducted with the use of sham HBOT to blind patients and assessors to the treatment allocation and screening to determine the effectiveness of the concealment process. The trial was multi-centred with procedures put in place to ensure standard practice between centres and included a reasonably large number of patients. As such these results, showing a statistically significant benefit for HBOT in treating radiation induced proctitis, can be considered fairly robust. The trial administered HBOT at 2.0 ATA on the grounds that this offered the best compromise between clinical effectiveness and safety. Higher oxygen pressures are reported in other studies for this indication but no evidence was identified which indicated that the use of such dosages would have been preferable.

Neither of the trials considering neurological indications\textsuperscript{118,119} demonstrated a benefit for HBOT in the outcomes assessed. Huslof et al.\textsuperscript{118} included a small number of subjects. The authors of the Cochrane review\textsuperscript{108} queried whether the lack of efficacy in the Pritchard et al.\textsuperscript{119} study could be due to lack of response of the nerve tissue to HBOT or because the patient group used had a long-standing condition.

Ohguri et al.\textsuperscript{116} considered prophylactic use of HBOT for neurological injuries. They failed to show a statistically significant HBOT benefit for radionecrosis, but did show non-HBOT use to be a predictor of radiation induced brain injury at 1 year. The patients in the HBOT group were significantly younger and had a significantly higher prevalence of primary controlled and brain only metastases than those in the control group. Given this and other inevitable biases in this non-randomised study, the results are best viewed as exploratory and suggest a need for further study.

The Marx study\textsuperscript{120} indicates a benefit in using HBOT in patients receiving major soft-tissue surgery or flaps to previously irradiated head or neck tissue. While this study included a large number of subjects (n=160) very few methodological details were available, as it is only reported in a textbook, making it difficult to establish the quality and validity of the findings.

The case series evidence, identified in reviews other than Bennett et al.\textsuperscript{108}, is fairly extensive and some review authors suggest that it may indicate a benefit for HBOT in patients with previous failure to heal. There is consistency among the studies that were prospective or included a historical control group. However the results were prone to bias and confounding and, whilst interesting and suggesting a need for further research, cannot be used as a basis for treatment recommendations.

Some conditions considered in the reviews are very rare, making it unfeasible to conduct adequately powered RCTs. In these cases, the use of registry databases in which all cases treated with HBOT are recorded according to standardised criteria provides an alternative approach. The data could then be compared with those from matched concurrent controls.

In summary, there is some evidence of a benefit of HBOT in treating radiation induced proctitis and for patients requiring head or neck surgery to previously irradiated tissue. There is insufficient evidence to determine whether HBOT is useful in treating late radiation tissue injury at other sites.
### Table 4.9-1  Evidence on using HBOT to treat soft tissue radiation injury - included studies

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<tr>
<th>Study</th>
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<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
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<td>Clarke et al., 2008</td>
<td>Multicentre randomised double-blind controlled trial</td>
<td>To evaluate the effect of HBOT for patients whose radiation proctitis had proven refractory to other interventions.</td>
<td>Population (n=75) Comparator (n=75) Air at 1.1 ATA, once daily, 5 times per week. Outcomes: Change in SOMA-LENT score; quality of life.</td>
<td>Patients who had undergone pelvic radiotherapy and had subsequently developed evidence of rectal late radiation tissue injury. Diagnosis present for ≥3 months and insufficient response to other therapies. Intervention: 100% oxygen at 2.0 ATA for 90 mins once daily, 5 times per week.</td>
<td>The improvement in SOMA-LENT score was 5.00 in the HBOT group versus 2.61 in the sham HBOT group (p=0.0019). There was a significantly greater proportion of HBOT-treated patients who experienced healing/improvement as clinically assessed OR=5.93 (95% CI 2.04 to 17.24). A sensitivity analysis on missing data values did not change the significance of these results.</td>
<td>Authors concluded that the use of HBOT for patients with chronic refractory radiation proctitis resulted in significantly improved and enduring healing responses and enhanced QOL.</td>
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<td>Ohguri et al., 2007</td>
<td>Retrospective case-controlled study</td>
<td>To evaluate the prophylactic effect of HBOT for radiation-induced brain injury in patients with brain metastases treated with SRS.</td>
<td>78 patients treated from Oct 1994–Sep 2003 at a Japanese hospital. HBOT group (n=32) non-HBOT group (n=46). Intervention: HBOT for 60 mins at 2.5 ATA, for a total of 20 sessions, 5 times per week.</td>
<td>Patients with brain metastases treated with SRS</td>
<td>Incidence of radionecrosis: HBOT=3, non-HBOT=2 (p=1.0). Incidence of white matter injury: HBOT=2, non-HBOT=9 (p=0.05). Multivariate analysis showed no significant association of HBOT with development of radionecrosis or white matter injury (p=0.07). Survival analysis showed that non-use of HBOT was a significant predictor of radiation-induced brain injury at 1 year (p=0.02).</td>
<td>There is potential value for prophylactic HBOT in radiation-induced white matter injury. No benefit was shown for radionecrosis. The HBOT arm included 11 patients with predictors of longer survival and those who had received prior or subsequent radiotherapy. The mean age of patients in the HBOT group was significantly younger and this group had significantly more primary controlled and brain only metastases.</td>
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| Bennett et al., 2005          | Cochrane systematic review | To assess the benefit and harm of HBOT in the treatment or prevention of late radiation tissue injury. | Comprehensive search of electronic databases, hand searching, expert opinion and reference list scanning. Search to mid 2004. | RCTs or pseudo-RCTs comparing the effect of a HBOT regimen on any late radiation tissue injury versus any treatment not including HBOT. All languages included. Included studies unless already considered for the assessment of osteoradionecrosis. | Clarke, 2004: Patients with problematic radiation proctitis (n=68)  
**Intervention**: HBOT at 2.0 ATA for 30–40 sessions over 6–8 weeks versus sham HBOT
**Results**: See individual entry for this trial.  
Hulshof, 2002: Patients with cognitive deficits present at least 1.5 years after brain irradiation (n=7)  
**Intervention**: HBOT at 3 ATA for 115 minutes for 30 sessions over 6 weeks. No comparator was specified.  
**Results**: No statistically significant difference in the number of improved neuropsychiatric tests was seen at 3 or 6 months.  
Pritchard, 2001: Patients with established radiation-related brachial plexopathy (n=34)  
**Intervention**: HBOT at 2.4 ATA, daily 5 times/week for 30 sessions. Control: sham HBOT.  
**Results**: Change in mean warm sensory threshold temperature 1 week after therapy - HBOT WMD=1.1 degrees lower (95% CI: -1.9, 4.1; p=0.47). Change in mean warm sensory threshold temperature 1 year after therapy. HBOT WMD=0.9 increase (95% CI: -2.3, 4.0; p=0.47). Resolution of swelling - HBOT RR=5.0 (95% CI: 0.26, 97.0). Improved quality of life (SF-36 score at 12 months – general health) - HBOT WMD=2.3 (95% CI: -18.95, 14.35). Improved quality of life (SF-36 score at 12 months – physical function) - HBOT WMD=4.0 (-19.40, 11.40).  
Marx, 1999: Patients requiring major soft-tissue surgery or flaps to an irradiated area of the head or neck (n=160).  
**Intervention**: HBOT for 20 pre-operative sessions at 2.4 ATA, 90 mins daily, 5 days/week. 10 postoperative sessions.  
**Results**: Wound dehiscence. Control versus HBOT RR=8.67 (95% CI: 2.73, 27.49). | The Marx 1999 study was described as randomised but no details were provided concerning blinding or allocation concealment. |
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<td>Pasquier et al., 2004 &gt;109</td>
<td>Systematic review</td>
<td>To study the effect of HBOT for radio-induced lesions in normal tissues (other conditions not discussed).</td>
<td>Limited search of electronic databases and reference list scanning. Search from 1960-2004.</td>
<td>included RCTs, non-controlled trials, retrospective studies, case reports. Laryngeal chondronecrosis - case series. Head and neck soft-tissue necrosis - case series. Rectum - case series. Bladder - case series, 1 prospective trial. Breast and chest wall injury - prospective case series, a phase II trial. Rectal and duodenal ulcerations, pelvic necrosis - several retrospective case series. Myelitis - 1 case report and 1 case series. Plexopathy - RCT (Pritchard et al., 2001) and one case report. Optic neuropathy - case series. Brain necrosis - retrospective case series including children.</td>
<td>Laryngeal chondronecrosis: all case series suggested benefit for HBOT. Head and neck soft tissue necrosis: poor level of efficacy evidence. Rectum: weak support for HBOT benefit. Bladder: case series suggest HBOT efficacy. Breast and chest wall injury: some benefit reported. Rectal and duodenal: beneficial action of HBOT weakly supported. Myelitis: benefit in the limited literature available. Plexopathy: Pritchard et al., 2001 (as above). Optic neuropathy: some benefit when HBOT is started early. Brain necrosis: no clear data.</td>
<td>Authors concluded that due to lack of controlled trials, failure to use acceptable outcome measurement scales, document time scales or specify endpoints it is difficult to interpret the evidence. For haemorrhagic cystitis although there are no RCTs, the results of prospective and retrospective studies suggests that HBOT is effective, leads to a high rate of bladder preservation and has few side effects.</td>
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<td>Wang et al., 2003</td>
<td>Systematic review</td>
<td>To determine if adjunctive HBOT is effective in hypoxic wounds (soft-tissue radionecrosis discussed)</td>
<td>Studies identified from technology assessment reports on HBOT updated by MEDLINE search 1998–2001. Expert opinion was included.</td>
<td>RCTs, non-randomised comparison studies and case series reporting original data, including at least 5 human subjects. HBOT used as adjunctive therapy to standard wound care. <strong>Included studies</strong> 13 case series, 1 using historical controls (Neovius, 1997).</td>
<td>All case studies reported benefit for HBOT. Neovius et al. 1997 Number of patients healing completely: HBOT 12 of 15, historical controls 7 of 15 (no calculation of statistical significance). Several case series reported that patients had failed to heal from standard treatments received before the trial (Mathews et al., 1997; Woo et al., 1997; Norkool et al., 1993; Williams et al., 1992).</td>
<td>Trials’ quality was poor, however the consistency of the findings suggests that HBOT may aid wound healing in soft-tissue radionecrosis.</td>
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<td>Medical Services Advisory Committee, 2003</td>
<td>Technology assessment report</td>
<td>To evaluate the safety and effectiveness of HBOT in management of non-healing wounds in refractory soft-tissue radiation injuries (other aims not discussed).</td>
<td>Comprehensive search of electronic databases, reference list scanning and expert opinion.</td>
<td>Patients with soft-tissue radiation injury, with refractory wounds who had failed on conventional therapy. HTAs, systematic reviews, meta-analyses, RCTs, controlled studies, cohort and comparative studies, case series if patients were enrolled consecutively or presented in a specified timeframe. Systematic reviews and RCTs in any language, with other studies in English only. Systematic reviews: Feldmier and Hampson, 2002. RCTs: Hulshof et al., 2002; Pritchard, 2001; Marx, 1994 (may be the same study as Marx 1999); Marx, 1985 (covered under ORN). Non-randomised comparative studies: Carl, 2001; Neovious, 1997. Case series: 9 studies.</td>
<td>Systematic reviews: Feldmier and Hampson, 2002 (see below). RCTs: Hulshof et al., 2002 (as above); Pritchard, 2001 (as above); Marx, 1994 (as above).</td>
<td>The clinical evidence does not substantiate the claim that HBOT is effective in the treatment of refractory soft-tissue radiation injury.</td>
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<td>Denton &amp; Maher, 2003</td>
<td>Systematic review</td>
<td>To evaluate treatment options addressing physical components of sexual dysfunction arising from pelvic radiotherapy, as prevention or treatment for acute or late complications (only HBOT assessed).</td>
<td>Comprehensive search of electronic databases, reference list scanning, hand searching and expert opinion.</td>
<td>RCTs, quasi-randomised trials, cohort studies, case control retrospective studies, longitudinal surveys and case histories. Studies of women with pelvic malignancy, who had received radiotherapy (primary or postoperative, with or without chemotherapy, or palliative). <strong>Included studies</strong>: 4 case series: 1 prospective and 3 retrospective.</td>
<td>All studies showed benefit for HBOT in cases of late pelvic radiation injury that had failed to respond to conventional treatment.</td>
<td>While the results appeared favourable to HBOT they were based upon weak evidence and therefore of limited validity.</td>
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<td>Denton et al., 2002</td>
<td>Systematic review</td>
<td>To identify the effect of HBOT in the management of late chronic radiation cystitis (other indications not considered here).</td>
<td>Comprehensive search of electronic databases, hand searching, reference list scanning and expert opinion, The search was recently updated to April 2007.</td>
<td>RCTs, quasi-randomised trials, cohort studies, case-controlled retrospective studies, longitudinal surveys and case histories in any language. Studies in which patients with pelvic malignancy had received radiotherapy and subsequently developed late radiation cystitis. <strong>Included studies</strong>: 19 case series, of which 1 was prospective.</td>
<td>No overall conclusions were possible. It was noted that the minimum reported response for the intervention was 60%, for a minimum duration of 2 months.</td>
<td>It was impossible to draw conclusions on the efficacy of HBOT for late radiation cystitis, given the lack of high quality evidence.</td>
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<td>Denton et al., 2002</td>
<td>Systematic review</td>
<td>To assess the effect of HBOT for managing late chronic radiation proctitis (other indications not considered here).</td>
<td>Comprehensive search of electronic databases, hand searching and reference list scanning, expert opinion. Search to 2001.</td>
<td>RCTs, quasi-randomised trials, cohort studies, case-controlled retrospective studies, longitudinal surveys and case histories. Patients with pelvic malignancy who had received radiotherapy, and subsequently developed late radiation proctitis. <strong>Included studies</strong> 8 case series, of which 1 was prospective.</td>
<td>No results presented due to the poor evidence quality.</td>
<td>HBOT may be of value for late radiation proctitis which is refractory to conservative treatment. Given the quality of evidence, it was not possible to quantify the degree of benefit.</td>
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<td>Feldmeier &amp; Hampson, 2002</td>
<td>Systematic review</td>
<td>To study the effect of HBOT in the prevention and treatment of delayed radiation injuries (only soft-tissue necrosis considered here).</td>
<td>Limited search of electronic databases, reference list scanning and conference abstracts. Search dates not reported.</td>
<td>Inclusion criteria not reported. Included studies Head and neck: 6 case series, 1 with historical control group (Neovius, 1997) and 1 prospective controlled study (Marx, 1999). Radiation cystitis: 17 case series, 1 of which was prospective (Bevers, 1995). Chest wall and breast: 4 case series, one with non-randomised control group (Carl, 2001). Radiation proctitis and enteritis: 10 case series; 2 case reports. Miscellaneous abdominal wall and pelvic injuries: 2 case series; 1 case report. Neurologic injuries: one RCT (Pritchard, 2001): 8 case series and 4 case reports. Radiation necrosis of the extremities: 1 case series and 1 case report.</td>
<td>Head and neck: Marx, 1999 (see above); Neovius, 1997 (see above) and other case series. Reported positive outcomes in patients treated with HBOT. Radiation cystitis: 16 of 17 case studies showed positive results for patients treated with HBOT. Chest wall and breast: all case series showed positive results for patients treated with HBOT. Radiation proctitis and enteritis: all showed positive results for HBOT. Miscellaneous abdominal wall and pelvic injuries: all showed positive results for HBOT. Neurologic injuries: Pritchard, 2001 (see above) and case series. Results indeterminate for myelitis, brain necrosis and optic neuritis. Radiation necrosis of the extremities: some benefit for HBOT.</td>
<td>Authors concluded that the consistency of the case series evidence available and lack of other treatments indicate that HBOT should be considered for late radiation tissue injuries.</td>
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<td>Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé, 2001&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Technology assessment report</td>
<td>To determine the efficacy and safety of HBOT in treatment of soft-tissue necrosis due to radiation therapy (other indications not considered here).</td>
<td>MEDLINE search and reference list scanning. Literature in English and French available to 1999 were included.</td>
<td>Included studies Controlled trials: Warren et al., 1997. Case series: various reported, including 1 with historical control group (Neovius et al., 1997) and 1 prospective study (Bevers et al., 1995).</td>
<td>Controlled trials: Warren et al., 1997. Both groups received HBOT but treatment regimens differed. Neovius, 1997 (as above).</td>
<td>HBOT showed promising results for soft-tissue necrosis, however only weak evidence is available.</td>
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<td>Ward et al., 2000&lt;sup&gt;115&lt;/sup&gt;</td>
<td>Systematic review</td>
<td>To evaluate evidence on the effectiveness of HBOT following radiotherapy for oral cancer (only promotion of wound healing considered here).</td>
<td>Electronic database search. No details provided.</td>
<td>Inclusion criteria not reported. Included studies 1 RCT (Marx, 1999).</td>
<td>Marx et al., 1985 (as above).</td>
<td>Concluded that the evidence does not provide a clear direction for treatment recommendations.</td>
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<td>ECRI, 1998&lt;sup&gt;107&lt;/sup&gt;</td>
<td>HTA</td>
<td>To study the use of HBOT in irradiation induced tissue damage.</td>
<td>Not reported.</td>
<td>Not reported. Several small case series included.</td>
<td>All case series showed positive results for HBOT. The case for using HBOT for soft-tissue radionecrosis is not clear. Additional larger controlled studies are required.</td>
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4.10 Osteoradionecrosis

Introduction

Osteoradionecrosis (ORN) is the bony manifestation of the late radiation tissue injury described in the previous section. The condition can take months or years to develop, may occur spontaneously or can be triggered by procedures on the area of irradiated bone. ORN can occur at different body sites but most commonly affects the mandible\textsuperscript{121}.

HBOT has been used to treat established osteonecrotic wounds and to prevent the development of osteoradionecrosis after surgical trauma in a previously irradiated area (eg, dental treatment). In treatment, it is used as an adjunct to good oral care, nutritional support and surgery, and is not practiced as an isolated therapy.

Evidence identified

Six HTAs\textsuperscript{8,10,11,107,108,122}, seven systematic reviews\textsuperscript{12,108,109,111,114,115,121} and one additional RCT\textsuperscript{123} met the inclusion criteria. The use of HBOT is discussed briefly in SIGN Guideline 90 ‘Diagnosis and management of head and neck cancer’\textsuperscript{124}. Numerous case series, case reports and observational studies on the use of HBOT for ORN of the mandible, skull, extremities, external auditory canal and pelvis were also identified. These were not included as they did not add to this evidence base and were susceptible to confounding and bias. Details of the studies included are presented in Table 4.10-1. Studies varied as to whether they considered the use of HBOT for prevention or treatment of ORN. While studies of ORN in any part of the body were eligible for inclusion, all primary studies included within the secondary literature and the two RCTs assessed ORN of the mandible.

Evidence quality

The HTAs and systematic reviews were all considered to be of acceptable quality, but some were more rigorous than others. The Cochrane reviews by Esposito et al.\textsuperscript{121} and Bennett et al.\textsuperscript{124} meet most assessment criteria. Other systematic reviews and HTAs failed to report inclusion or exclusion criteria\textsuperscript{114}, details of literature search methodology or the methodology used to assess evidence quality\textsuperscript{11,107,115}. The Annane et al.\textsuperscript{123} RCT included a power calculation and was double blinded.

Despite variations in the rigour with which the secondary studies were conducted, all identified the same small number of primary studies. The main quality issues related to the conduct of primary studies rather than the methodology of the secondary studies. The secondary study authors reported that the primary studies were of poor methodological quality and varied considerably in patient inclusion criteria, treatment protocols, and measurement and reporting of outcomes.

Results

HBOT is used for both the prevention of ORN and treatment of pre-existing ORN; the evidence for these two applications is considered separately.

Prevention of ORN following dental therapy in an irradiated area

The Cochrane review by Esposito et al.\textsuperscript{121} included one RCT which assessed the efficacy of HBOT in improving various clinical, radiological and quality of life related outcomes in patients with previous irradiation for head or neck cancers and receiving implant-retained lower dentures. No statistically significant differences in prosthesis or implant failure, postoperative complications or patient satisfaction were observed between the group receiving HBOT therapy compared with those who did not.

Other secondary studies all included the same randomised trial undertaken by Marx\textsuperscript{125}. In Marx\textsuperscript{125}, the efficacy of HBOT was compared with antibiotic therapy for preventing the development of osteonecrosis in patients who had previously received radiation therapy to the head or neck and required tooth extraction. Patients receiving HBOT had a statistically greater likelihood of healing of the tooth sockets than those receiving antibiotic prophylaxis (RR=1.4, 95% CI: 1.1, 1.7; p=0.009).

Several secondary studies described a case-controlled trial\textsuperscript{26} considering the efficacy of HBOT prior to placement of dental implants. The percentage of implants failing in the HBOT group was significantly lower than in patients not receiving HBOT (8.1% versus 53.7%; p=0.0009).

Treatment of ORN

Bennett et al.\textsuperscript{124} identified a trial\textsuperscript{127} reporting on 104 patients requiring hemimandibular reconstruction on previously irradiated jaws. The group receiving HBOT therapy had a statistically greater chance of bony continuity being established (RR=1.4; 95% CI: 1.1, 1.8; p=0.001). Several secondary studies identified one RCT\textsuperscript{128} that considered healing of jaw ORN. This was a preliminary study and no quantitative results were given, however the authors reported that there was ‘significant improvement of healing progress in the HBOT group according to X-ray interpretation, and clinical signs and symptoms’.

One recent RCT\textsuperscript{123}, published after the secondary studies, randomised patients with a history of radiation and overt mandibular ORN to receive either HBOT or sham HBOT. Patients with the more severe forms of ORN were excluded. The trial considered that treatment was a failure if the ORN was not healed or the patient required surgery at assessment. Thus this trial tested the efficacy of HBOT as a primary therapy for ORN. The primary outcome measure was the number of patients with no evidence of ORN at 1 year, but those cases with <20 mm of exposed bone on entry, but that had required surgery were excluded. At that time, 19% of the HBOT group had recovered compared with 32% of the control group (RR=0.6%; 95% CI: 0.25, 1.41).

The SIGN guideline on diagnosis and management of head and neck cancers used similar supporting evidence on ORN to that discussed above and made a level C recommendation that HBOT should be available for selected ORN patients.
Discussion

Prevention of ORN following interventional procedures

The study by Marx et al. was carried out some time ago and was not blinded but provided the main evidence for this indication. The case-controlled study offered some support for use of HBOT but, in the absence of randomisation, the strength of the findings are limited. Some reviews cite case series that further support the use of HBOT in this area.

The recently conducted RCT identified in the Esposito et al. review had potential to provide more robust evidence in this area, however the study was underpowered and too small to show meaningful differences between treatment groups, and as noted by the review authors, was highly susceptible to bias.

The evidence in this area is very limited and conflicting. HBOT may show some promise in preventing the development of ORN following dental treatment, but higher quality studies need to investigate this in more detail.

Treatment of ORN using HBOT

Evidence relating to the use of HBOT to treat ORN is even more limited. There is insufficient detail available for one of the RCTs identified by the secondary literature and the other was a pilot study and reported only limited results. Some case series support the use of HBOT for treatment of ORN. On the basis of the RCT and a physiological basis for treatment, the secondary literature generally concluded there may be a benefit to using HBOT to treat ORN but more research is required.

The results of the RCT by Annane et al. suggested that patients with ORN experienced worse outcomes when receiving HBOT, although the difference was not statistically significant. This study was originally powered to show a difference between groups but was stopped early leaving it underpowered. As such the results cannot be considered definitive. Some experts have argued that the best available treatment for mandibular ORN includes a multi-disciplinary approach and that considering progression to surgery as treatment failure is unrealistic and does not reflect practice.

Whilst it is plausible that HBOT may aid treatment of ORN, given the evidence base it is impossible to say whether benefit will be seen in the clinical setting. A multinational double-blind RCT (HORTIS) to determine the degree of benefit that HBOT affords in late radiation tissue injury is ongoing. This study has eight component trials, with seven considering the use of HBOT at various anatomic sites including the mandible. The eighth considers HBOT as a prophylactic therapy for late radiation tissue injury. The study aims to recruit 500 patients and will complete in 2010, further details are available from www.clinicaltrials.gov (study identifier no. NCT00134628).
Esposito et al., 2008. Systematic review. To compare dental implant treatment carried out with and without HBOT in irradiated patients.

- Comprehensive search of electronic databases, hand searching, scanning bibliographies, contacting experts. Last search undertaken on 13 June 2007.

Inclusion/exclusion criteria:
- RCTs with patients who have had radiotherapy and who have teeth that require replacement with osseointegrated dental implants. Conducted in any language included.

Results:
- RCT: Schoen, 2007. Intervention (n=13): 20 HBOT treatments of 100% oxygen at 2.5 ATA for 80 mins before implant surgery, and 10 similar treatments after surgery, in addition to antibiotic prophylaxis.
- Comparator (n=13): antibiotic prophylaxis.
- One year after delivery of the prosthesis, there were no statistically significant differences for any outcome measures.

Conclusions and comments:
- HBOT was not shown to enhance implant survival in the radiated mandibular jaw bone. However, patient numbers were small and the study was probably underpowered to show a difference.
- The review authors considered that there was a high risk of bias in the one included study.
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<td>Bennett et al., 2005</td>
<td>Cochrane systematic review</td>
<td>To assess the benefit and harm of HBOT for the treatment or prevention of late radiation tissue injury (only ORN assessed).</td>
<td>Comprehensive search of electronic databases, reference list scanning, hand searching and expert opinion. Electronic databases searched to mid 2004.</td>
<td>RCTs and pseudo-RCTs that compared a regimen including HBOT with any treatment not including HBOT. All languages included. Included studies Marx, 1985; Marx, 1999a.</td>
<td>RCTs: Marx, 1985. 74 patients requiring tooth extraction in a field irradiated with ≥6000 cGy 6 months–15 years previously. Intervention: 20 preoperative HBOT sessions at 2.4 ATA for 90 mins daily for 5 or 6 days a week, followed by 10 post-operative sessions. Comparator: Standard tooth extraction with 1 million units penicillin pre-extraction and 500mg 4 times each day for 10 days post-extraction. Results: Healing of tooth sockets following extraction in irradiated field at 6 months: HBOT 35 of 37 and control 26 of 37 patients achieved healing in all sockets (RR 1.4; 95% CI: 1.1, 1.7; p=0.009). Marx, 1999a. 104 patients requiring hemimandibular jaw reconstruction in tissue beds exposed to ≥6400 cGy radiotherapy. Intervention: 20 preoperative HBOT treatment sessions at 2.4 ATA for 90 mins daily 5 days/week, followed by 10 postoperative sessions. The comparator was not specified. Results: Establishment of bony continuity: HBOT 48 of 52 achieved continuity, control 34 of 52 achieved continuity (RR 1.4; 95% CI: 1.1, 1.8; p=0.0001). Marx, 1985 and 1999a. Achievement of complete mucosal cover: HBOT 83 of 89, control 60 of 89 (RR 1.4; 95% CI: 1.2, 1.6; p&lt;0.001).</td>
<td>There is some evidence that HBOT improves outcome in late radiation tissue injury affecting bones of the head, and prevents the development of ORN following tooth extraction in a irradiated field. Results are limited by the small number of studies, and poor methodological quality. Only a sketchy account within a textbook is available for the Marx 1999 study. Neither Marx study was blinded.</td>
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<td>Annane et al., 2004[1,2]</td>
<td>RCT</td>
<td>To determine the efficacy and safety of HBOT for mandibular ORN.</td>
<td>Patients had one of various prespecified clinical and radiographic criteria. Before randomisation, patients were assigned to group A or B based on ORN severity. Intervention: HBOT group A, 30 exposures at 2.4 ATA for 90 mins, 5 days/week over 3 consecutive weeks. HBOT group B As above with surgical treatment and 10 additional HBOT treatments, 1–3 weeks after surgery. Comparator: Placebo HBOT with 9% oxygen and 91% nitrogen. All received conservative treatment of analgesics, antibiotics and debridement. Outcomes: Primary outcome was number of patients who had recovered from ORN at 1 year. This included group A patients, not progressing to surgery.</td>
<td>Patients with a history of radiation with overt mandibular ORN, ≥2 months after optimal conservative treatment including antibiotics, irrigation and surgery.</td>
<td>Recovery at 1 year HBOT 6 of 31 (19%) Control 12 of 37 (RR 0.6; 95% CI: 0.25, 1.41; p=0.23). 222 patients were required to detect an HBOT difference of at least 20%. The study was stopped prematurely following a prespecified sequential procedure that showed no evidence for HBOT superiority. Patients with more severe mandibular radionecrosis were not included. As the need for surgical care indicated treatment failure in group A patients, failure rates appeared higher than in other studies which included surgery as part of the treatment regimen.</td>
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</table>
Pasquier et al., 2004

**Study Type**: Systematic review

**Aim**: To study the effect of the treatment of osteoradionecrosis (ORN) induced lesions in normal tissues (only ORN is assessed here).

**Search strategy/characteristics**

- Search strategy: Electronic databases to 2004 and reference list scanning.
- Inclusion/exclusion criteria: ORN treatment: only case studies identified. Oral infections and complications and tooth extraction: Marx et al. (as above). Several case series were presented narratively.

**Results**

1. Patients with endosseous implants who underwent irradiation prior to surgery (n=32).
2. After irradiation received HBOT at 2.5 ATA for 90 mins for 20 sessions, followed by surgery. After surgery patients received 10 HBOT sessions (n=20).
3. HBOT protocol as above for group receiving reimplanted devices (n=10).

**Outcomes**: % of implants failing

- Group 1 HBOT=8.1%
- Group 2 HBOT=3.7%
- Group 3 Remplanted devices=3.8%

**Conclusions and comments**

Based on the proportion of patients improving in retrospective case series HBOT may be effective in the treatment of mandibular ORN where conservative treatment proves insufficient. There was some evidence for benefit of HBOT in the prevention of ORN. More research is needed on using HBOT to reduce implant loss. The number of patients developing ORN in the control arm of the Marx et al., 1985 study was surprisingly high.
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<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
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<tr>
<td><strong>Wang et al., 2003</strong></td>
<td>Systematic review</td>
<td>To determine efficacy of adjunctive HBOT for hypoxic wounds (only ORN discussed)</td>
<td>Studies identified from technology assessment reports on HBOT, MEDLINE search from 1998–2001 and articles suggested by expert reviewers.</td>
<td>RCTs, non-randomised comparison studies, and case series that included at least 5 human subjects. RCTs: Marx et al., 1985; Tobey et al., 1979. Case series: McKenzie et al., 1993.</td>
<td>Marx et al. (as above). Tobey et al., 1979. Preliminary report does not give quantitative results. States 'significant improvement for healing progress in HBOT group according to X-ray, clinical signs and symptoms'.</td>
<td>Evidence was limited but HBOT may aid wound healing in ORN.</td>
</tr>
<tr>
<td><strong>Feldmeier &amp; Hampson, 2002</strong></td>
<td>Systematic review</td>
<td>To study the effect of HBOT in prevention and treatment of delayed radiation injuries (only ORN considered here).</td>
<td>Searching of electronic databases and reference list scanning.</td>
<td>Inclusion/exclusion criteria not reported. Included studies Prevention of mandibular ORN RCT: Marx et al. 1985. Case series: David et al., 2001; Vudiniabola et al., 1999. Treatment of existing mandibular ORN RCT: Tobey et al., 1979. Case series: 12 studies undertaken from 1975–2001 (included 12–70 patients).</td>
<td>Prevention of mandibular ORN: Marx et al. (as above). Treatment of existing mandibular ORN: Tobey et al. (as above). 12/13 case studies indicated that HBOT was likely to be beneficial.</td>
<td>Authors concluded that HBOT is beneficial for the prevention of mandibular ORN and is likely to be beneficial for its treatment.</td>
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<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
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<td>Saunders, 2000&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Systematic review</td>
<td>To assess the effectiveness of HBOT in treatment of conditions of significance in West Midlands and determine whether there was a case for establishing an HBOT unit in the region (only ORN assessed here).</td>
<td>Comprehensive search of electronic databases from 1968–2000. Additional attempts to identify papers included hand searching, reference list scanning and expert opinion.</td>
<td>All language and study designs included. Included studies RCTs: Marx et al., 1985; Tobey et al., 1979.</td>
<td>As above.</td>
<td>There is no convincing evidence that HBOT is of benefit for ORN although there is a physiological basis for an effect.</td>
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<tr>
<td>Study</td>
<td>Type</td>
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  Included studies  
  RCT: Marx et al., 1985.  
  Treatment of ORN  
  A small number of retrospective case series (not listed).  
  Marx et al., 1985 (as above). | Marx et al., 1985 (as above).  
  The weight of evidence supports the use of HBOT for the treatment of ORN but it may not be necessary for all patients. The evidence on ORN prevention is unclear. |
| Medical Services Advisory Committee, 2001      | HTA                | To evaluate HBOT safety and effectiveness in the treatment of a number of conditions. | Electronic database search, grey literature, expert opinion and reference list scanning.  
  Included studies  
  RCTs: Marx et al., 1985.  
  Case-controlled study: Granstrom et al., 1999.                                                                                       | Marx et al., 1985 (as above).  
  Granstrom et al., 1999 (as above).  
  The study was non-randomised and masking and loss to follow up were not described.                                                            |
| Study                                      | Type | Aim                                                                 | Search strategy/ characteristics                                                                 | Inclusion/exclusion criteria                                                                 | Results                                                                                                                                                                                                 | Conclusions and comments                                                                                       |
|-------------------------------------------|------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mitton & Hailey, 1998¹                   | HTA  | To provide advice to the Calgary Region Health Authority on the effectiveness of HBOT and the impact of introducing an additional facility. | Comprehensive search of electronic databases, reference list scanning and expert opinion. Included studies to 1997. | HBOT considered for 13 conditions recommended by the UHMS. Studies with low-level evidence were excluded when higher level evidence was available. | Authors reported promising results for HBOT but stated that further studies are needed to clearly establish effectiveness. | A hypothetical control group was used by Dempsey et al., 1997.                                               |
| ECRi, 1998²                              | HTA  | To study the use of HBOT in the treatment of irradiation induced tissue damage (mandibular radionecrosis). | Not reported.                                                                                     | Not reported.                                                                                                                                  | Several small case series reported.                                                                                                                                        | The evidence is currently inconclusive.                                                                         |
| British Columbia Office of Health Technology Assessment, 1992² | HTA  | To assess the use of HBOT for ORN (other aims not assessed here). | Limited search of electronic databases and reference list scanning. Search from 1988-1991. | Included case series, controlled trials and RCTs. Marx et al., 1985. Several case series reported.                                                                 | Marx et al., 1985 (as above). Case series consistently reported a reasonable level of success.                                                                 | HBOT may be a useful adjunct to surgery post-irradiation of the mandible, however further research is needed. |
4.11 Cancers and tumour sensitisation

Introduction

Many solid tumours contain hypoxic areas that can be resistant to radiation therapy. The administration of HBOT can raise the pressure of oxygen in such areas, so the simultaneous use of HBOT and radiotherapy is postulated to improve the sensitivity of tumours to radiotherapy, resulting in a higher likelihood of anti-tumour efficacy. Adjunctive use of HBOT has also been suggested to improve the sensitivity of tumours to chemotherapy and is also considered in this section.

Evidence identified

Three HTAs and two systematic reviews met the inclusion criteria for this indication. One additional pilot RCT, published since the date of the last review was retrieved. AHRC included the AETMIS HTA and both systematic reviews, but did not undertake quality assessment or include additional material. Consequently this study was not considered further and the other HTAs and systematic reviews were used as the evidence base.

Various cancers were considered within the HTAs and reviews. Most evidence related to head and neck cancers, and cancer of the uterine cervix and bladder. A small amount of evidence was available concerning lymphoma, lung cancer and neuroblastoma. Most studies considered the use of radiotherapy although a small number, including the recent RCT, described chemotherapy with or without radiotherapy. Details of the included studies are presented in Table 4.11-1.

Evidence quality

The Cochrane review was considered well conducted with extensive efforts made to identify literature and minimise bias. The MSAC HTA was also robust in its conduct, although it included only trials published in English. Widmark et al. was based upon a limited literature search and did not report details of quality assessment of the primary literature. Similarly, the literature search in the AETMIS HTA was limited and only included studies in English or French, and details of quality assessment were not reported.

Despite the variability in the robustness of the reviews they mainly identified the same primary studies. The small number of primary studies and their low methodological quality, rather than the conduct of the secondary research, compromised the overall quality of the evidence.

The additional RCT identified was undertaken as a pilot study and was mainly concerned with the mode of action and safety of HBOT in conjunction with chemotherapy, rather than efficacy. As such the trial was small and considered few patient-related outcomes; while details of the study are included in Table 4.11-1, it will not be discussed further here.

Results

Head and neck cancers

Bennett et al. provided the most recent and well-conducted review of the literature on head and neck cancers, and captured all trials included in earlier reviews. The authors identified 10 RCTs or pseudo-RCTs conducted from 1968–1999, including 785 patients. Statistical pooling of the outcomes of these trials was undertaken using fixed-effects model where there was little evidence of heterogeneity between trials, and random-effects model where significant heterogeneity existed. Mortality at 1 and 5 years after treatment was significantly lower in patients receiving HBOT in addition to radiotherapy. The 1-year finding was, however, sensitive to the effect of patient withdrawal from the study. At 5 years, prespecified subgroup analysis suggested that benefit was restricted to patients who received a radiation fractionation scheme (dosage spread) of 12 or fewer ‘high dose’ sessions, compared with those who had a more conventional number of sessions, each at a lower dose. No significant difference in mortality at 2 years was observed. There was a statistically significant improvement in local tumour control at 3 months and in controlling local recurrence at 1 and 5 years. Again subgroup analysis suggested that the benefit at 5 years may be restricted to those receiving 12 or fewer radiotherapy sessions.

Bladder cancer

Bennett et al. identified five RCTs or pseudo-RCTs undertaken from 1967–1978, which included 343 patients. Statistical pooling of outcome measures from these trials using fixed-effects models failed to show statistically significant survival benefit at 1, 2 or 5 years for patients treated with adjunctive HBOT with radiotherapy alone. The review by Widmark et al. assessed three trials and MSAC report four trials, with two in common with Bennett et al. The additional trials were excluded by Bennett et al. on the basis that they were fully reported in a later included study. As a result, these other reviews do not provide additional evidence.
Lymphoma

MSAC identified one small Chinese trial published in 1993, in which the intervention group received HBOT as an adjunct to chemotherapy. The trial was considered methodologically weak by the review authors, but showed statistically significant reductions in tumour area, complete remission time, some haematological measures and in bone marrow cells for patients receiving HBOT. These patients also experienced statistically significant increases in remission rate, remission and survival duration.

Lung cancer

MSAC identified one single-centre trial from the USA, comparing the effect of adjunctive HBOT versus exposure to air with radiotherapy in patients with lung cancer. Little methodological detail was provided to allow the quality of the study to be assessed, but study conduct appeared inadequate in a number of areas. No statistically significant differences were found in survival rates between the two groups.

Neuroblastoma

MSAC identified one case series, with historical controls, showing improved survival for the HBOT-treated group.

Metastatic disease

Bennett et al. reported no benefit for adjunctive HBOT at reducing the incidence of metastatic disease at any anatomical site.

Adverse effects

Bennett et al. report a significant increase in the rate of severe radiation injury and risk of seizures in patients receiving adjunctive HBOT compared with those receiving radiotherapy alone.

Discussion

While HTAs and systematic reviews identified more RCTs and controlled trials for this indication than others in this report, the evidence base was still limited by poor reporting and methodological quality. It was notable that all studies except for the recent RCT, a pilot study, were undertaken before 2000 and no high-quality evidence has been forthcoming since.

The available evidence suggests that HBOT does confer some benefit in terms of reduced mortality, local tumour control and reduced tumour recurrence for head and neck cancers, and in reduced tumour recurrence for cancer of the uterine cervix. However, the results of the subgroup analysis of mortality at 5 years suggest that there is some doubt over whether the benefit observed was associated with the radiation fractionation scheme used rather than HBOT. It is important that the contribution HBOT can make is therefore assessed against the most effective fractionation scheme in air.

No evidence of a significant improvement in any outcomes assessed for bladder cancer were noted but, in the absence of high-quality studies, it is not possible to make firm conclusions concerning HBOT benefit for this indication. The lack of evidence relating to lymphoma, lung cancer and neuroblastoma also limits conclusions regarding the use of HBOT for these indications.

There appear to be significant risks for cancer patients receiving HBOT in combination with radiotherapy. This makes the need for further research to accurately quantify the benefits and risks more important.
Heys et al., 2006

Pilot RCT

To determine whether HBOT pre-treatment could modulate clinical and pathological responses in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy.

Patients with large primary breast cancers but without metastatic disease and under 75 years.

Intervention (n=15): 6 pulses of CVAP chemotherapy plus 10 HBOT sessions for 90 mins at either 2.4 or 2 ATA versus chemotherapy alone (n=17).

No significant difference in mortality rate between groups (p=0.69).

Other non-patient related outcomes were measured but not considered applicable to this report.

No modulation of the effect of neoadjuvant chemotherapy was seen with HBOT.

Table 4.11-1 Evidence on using HBOT as an adjunctive therapy for various cancers - included studies

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<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
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<tr>
<td>Heys et al., 2006</td>
<td>Pilot RCT</td>
<td>To determine whether HBOT pre-treatment could modulate clinical and pathological responses in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy.</td>
<td>Patients with large primary breast cancers but without metastatic disease and under 75 years.</td>
<td>No significant difference in mortality rate between groups (p=0.69). Other non-patient related outcomes were measured but not considered applicable to this report.</td>
<td>No modulation of the effect of neoadjuvant chemotherapy was seen with HBOT.</td>
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<td>Study</td>
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<td>Raman et al., 2006¹</td>
<td>Technology assessment report</td>
<td>To investigate the use of HBOT in the sensitisation of cancers and tumors to radiation therapy (other conditions not assessed here).</td>
<td>Comprehensive search of electronic databases and reference list scanning. No individual studies on the use of HBOT in cancers published after 1999 were found. Quality assessment: Studies were not critically appraised to determine validity.</td>
<td>Inclusion criteria: Studies of any size and design, including systematic reviews with or without meta-analysis, RCTs, non-randomised comparative, cohort and case controlled studies, retrospective case series and case reports of any clinical endpoint and intermediary outcome. Exclusion criteria: Studies in animals or evaluating HBOT in healthy humans. Foreign language articles, narrative reviews, commentaries and letters.</td>
<td>1 report (AETMIS, 2001) and 2 systematic reviews (Bennet, 2005; Widmark, 2003) were used. Cancer of uterine cervix: 2 RCTs: 1 showed no benefit; 1 showed significant improvement in locally advanced tumors in patients of less than 55 years. Bladder cancer: RCT: 1 showed no benefit. Head and neck cancer: 2 RCTs: in experimental stage. Systematic reviews: assessed whether HBOT improved the killing of hypoxic cancer cells by radiotherapy. Bennet, 2005 assessed: 19 trials, 2,286 patients: 785 with head and neck cancers, 1,089 with carcinoma of the cervix, 343 with bladder carcinoma. Others included bronchus, glioblastoma, rectum and oesophageal cancer. Head and neck tumors: mortality reduction at 1 (RR 0.83; 95% CI: 0.70, 0.98) and 5 (RR 0.82; 95% CI: 0.69, 0.98) years and improved local tumor control. Uterine cancer of the cervix: local tumor recurrence was lower at 2 years (RR 0.60; p=0.04). The effect varied with different radiotherapy schemes. Widmark, 2003 assessed 3 RCTs on HBOT + radiation for bladder cancer.</td>
<td>The use of HBOT does not offer benefit in the treatment of cancer. Bennet et al. concluded that some evidence indicates that HBOT has benefit as an adjunctive treatment in certain cancers. Widmark concluded that HBOT did not improve the efficacy of radiotherapy in muscle invasion cancer.</td>
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<td>Study</td>
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<td>Bennett et al., 2005</td>
<td>Systematic review</td>
<td>To assess the benefit and harm of radiotherapy with HBOT for tumor sensitisation.</td>
<td><strong>Search strategy</strong> Comprehensive search of electronic databases, reference list scanning, experts opinion and hand searching. Search conducted in November 2004. Quality assessed for internal validity using an adaptation of the Schulz 1995 method. <strong>Analysis</strong> Meta-analysis, fixed-effects model when no evidence of heterogeneity, random-effects model when heterogeneity was seen.</td>
<td>Patients receiving radiation therapy for solid tumors. No restrictions on age or gender. Study design: RCTs or quasi-randomised trials comparing the effect of simultaneous HBOT and radiation therapy versus radiation therapy while breathing air or the effect of HBOT with radiation therapy versus another sensitising therapy with radiation. Intervention: HBOT administered in a compression chamber at a pressure above 1.0 ATA simultaneously or immediately after radiation therapy. Outcomes: Primary outcomes: Mortality rate, complete or partial failure to control tumor, local recurrence rate, metastatic disease. Secondary outcomes: QOL, adverse effects, acute tissue reaction in irradiated area, late tissue injury in irradiated area, pain. HBOT adverse effects: visual disturbance, barotrauma, oxygen toxicity and others.</td>
<td>19 trials published from 1967–1999 (2,286 patients, 1103-HBOT and 1,153 control). <strong>Head neck cancers</strong> Mortality at 1 year: RR 0.83 (95% CI: 0.70, 0.98; p=0.03). The result was sensitive to patient withdrawal. Mortality at 5 years: RR 0.82 (95% CI: 0.69, 0.98; p=0.03). Subgroup analysis suggested that benefit may be restricted to patients receiving ≤12 fractions. Failure to control local tumors at 3 months: RR 0.58 (95% CI: 0.39, 0.85; p=0.006). Failure to control local recurrence at 1 year: RR 0.66 (95% CI: 0.56, 0.78; p&lt;0.0001). Failure to control local recurrence at 5 years: RR 0.77 (95% CI: 0.62, 0.95; p=0.01). Subgroup analysis suggested that benefit may be restricted to those receiving ≤12 fractions. <strong>Uterine cervix cancers</strong> Local tumor recurrence at 2 years: RR 0.60 (95% CI: 0.38, 0.97; p=0.04). Subgroup analysis suggested that benefit may be restricted to those receiving ≤12 fractions. Incidence of metastatic disease: no advantage of HBOT at any anatomical site. <strong>Adverse effects</strong>: significant increase in severe radiation injury (RR 2.35; 95% CI: 1.66, 3.33; p&lt;0.00001) and likelihood of seizures (RR 6.76; 95% CI: 1.16, 39.3; p=0.03) with HBOT.</td>
<td>There was some evidence that HBOT improved local tumour control and mortality for cancers of the head and neck. There was some evidence that HBOT reduced the chance of local tumour recurrence in cancers of the head, neck and uterine cervix. These benefits may be associated with the radiotherapy scheme used. Significant adverse effects such as oxygen toxic seizures and severe radiation injury were seen.</td>
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<td>Study</td>
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<tr>
<td>Widmark et al., 2003</td>
<td>Systematic review</td>
<td>To study the effect of HBOT in combination with radiation therapy in urinary bladder cancer.</td>
<td>Search strategy: MEDLINE, Cochrane library. Quality assessment not reported.</td>
<td>RCTs 1966–2001, systematic reviews with or without meta-analysis, prospective studies, case control and cohort studies (1990–2001). Studies evaluating side effects reports with less than 50 subjects were included. Exclusion criteria: Letters, editorials, case reports, non-RCTs, studies with patients with bilharzial bladder cancer, RCTs on neoadjuvant, concomitant and adjunctive chemotherapy in muscle invasive bladder cancer and studies with less than 50 subjects for efficacy outcomes.</td>
<td>33 articles were included. Of these 3 RCTs evaluated the effect of HBOT combined with radiation therapy in bladder cancer (Cade et al., 1978; Dische et al., 1973; Plenk et al., 1972). 2 studies showed that HBOT treatment did not improve survival (Cade, 1978; Dische, 1973). However early results of 1 small study showed survival improvement (Plenk, 1972).</td>
<td>There is fairly strong evidence that radiation therapy with adjunctive HBOT in bladder cancer does not confer treatment benefit. HBOT did not improve the efficacy of radiotherapy in muscle invasive bladder cancer.</td>
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<td>Study</td>
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<tr>
<td>Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé, 2001</td>
<td>Technology assessment report</td>
<td>To determine the efficacy and safety of HBOT in the treatment of various conditions (malignant diseases considered here).</td>
<td><strong>Search strategy</strong> MEDLINE search and reference list scanning. Literature in English and French to 1999. Quality assessment undertaken but no report of how performed.</td>
<td>Inclusion and exclusion criteria not reported.</td>
<td>3 RCTs (Cade et al., 1978; Watson et al., 1978; Fletcher et al., 1977).</td>
<td>Evidence suggests no additional benefit for HBOT as an adjunctive treatment for malignant tumours.</td>
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</table>
Medical Services Advisory Committee, 2001

**HTA**

To evaluate HBOT safety and efficacy in treating a number of conditions (only cancer covered here).

**Search strategy**


**Inclusion/exclusion criteria**

English language only. Trials with a control group.

**Results**

**Head and neck cancer**: (9 studies: 5 RCTs, 2 pseudo-RCTs and 2 comparative studies). Two studies showed a significantly better 5-year survival rate after HBOT and radiotherapy. 3 studies showed no difference in 5-year survival rate. Other studies showed no difference in shorter term survival. Five studies showed improvement in local tumour control rates with HBOT and 1 study found no difference.

**Cervical cancer**: (6 studies: 5 RCTs and 1 comparative study). 4 RCTs found no statistically significant survival benefit for HBOT.

**Bladder cancer**: (4 RCTs). 3 studies found no statistically significant difference in survival. 1 study reported survival benefit for HBOT.

**Lymphoma**: (1 pseudo-RCT). Those receiving HBOT had statistically significant reductions in tumour area, complete remission time, some haematologic measures and in bone marrow cells. There were statistically significant increases in remission rate, remission duration and survival duration.

**Lung cancer**: (1 RCT). No statistically significant differences were seen in survival rate, however little detail was available of the study conduct and methodology.

**Neuroblastoma**: (1 case series with historical controls).

**Conclusions and comments**

**Head and neck cancers**

Studies varied in design, patient populations and therapies used, and conflicted in outcomes and conclusions. There was a lack of quality studies to support the use of HBOT in head and neck cancers and little evidence of benefit.

**Cervical cancers**

There was insufficient evidence to determine the effectiveness of adjunctive HBOT. Studies varied in intervention and comparator protocols, methodology was poorly described and substantial use was made of post-hoc comparisons.

**Bladder cancer**

The results on survival benefit of using adjunctive HBOT were conflicting. Variations in methodological rigour and protocols made assessment difficult.

**Lymphoma**

One study provided an indication of benefit, however it was methodologically weak and stronger evidence is required.

**Lung cancer**

Little evidence was available and further studies are required.

**Neuroblastoma**

There was some evidence of effectiveness from a case series. Until more rigorous evidence is available, use of the technology cannot be supported.
4.12 Orthopaedics

This section discusses conditions which fall under the speciality of orthopaedics that are not already covered within the sections describing wounds, soft tissue, muscle injuries or other conditions. This section includes consideration of fracture healing, osteonecrosis and osteomyelitis.

Evidence identified

One Cochrane systematic review assessing the effect of HBOT on fracture healing\textsuperscript{135} was identified. Two secondary studies examining the use of HBOT for treating osteonecrosis, one an HTA\textsuperscript{136} and one a systematic review\textsuperscript{137} were identified. The latter was in German, however an executive summary was available in English and provided sufficient detail to allow inclusion of this study. A rapid systematic review\textsuperscript{138}, two earlier systematic reviews and an HTA\textsuperscript{6,111,122} were identified which covered osteomyelitis.

No additional studies, other than case studies, assessing HBOT in these indications were identified. Details of the evidence identified are presented in Table 4.12-1.

Evidence quality

The Cochrane review\textsuperscript{135} made rigorous attempts to identify literature, and provided a comprehensive description of intended methodology. The literature search conducted for the HTA report\textsuperscript{136} was also comprehensive and the methodology used was adequately reported. From the limited information available in the executive summary, the German systematic review\textsuperscript{137} appears to have been robust in its methodology. The review by Lawson\textsuperscript{138} was intended as a short pragmatic review of major sources of published literature but it appeared to have involved a thorough literature search and was explicit in its inclusion and exclusion criteria. Similarly the report by MSAC adopted a comprehensive approach to identifying and assessing the evidence. Both the Wang et al.\textsuperscript{111} review and the British Columbia\textsuperscript{122} report were more limited in the searches undertaken.

Results

Bennett \textit{et al.}\textsuperscript{135} did not identify any randomised or quasi-randomised controlled trials on the use of HBOT in fracture healing that met the inclusion criteria.

Regarding osteonecrosis, the German systematic review\textsuperscript{137} did not identify any controlled trials that met their inclusion criteria. Liu \textit{et al.}\textsuperscript{136} employed wider selection criteria and identified two observational studies. They reported the results of these studies separately due to differences in patient populations, treatment regimens and outcomes. One study was carried out in a paediatric population and was not considered in this review. Liu \textit{et al.}\textsuperscript{136} noted that resolution of hip necrosis was observed in the majority of cases in the second study, with the results comparing favourably with those seen in patients in another study of similar stage hip avascular necrosis. However, in the absence of a proper control group few conclusions could be drawn.

The rapid systematic review\textsuperscript{138} on HBOT for osteomyelitis included the two other systematic reviews\textsuperscript{6,111} and all identified the same small non-randomised, non-blinded trial comparing adjunctive HBOT with no hyperbaric treatment in patients with osteomyelitis. Likewise the British Columbia HTA identified only this trial. This single study provided insufficient evidence to assess the safety and efficacy of HBOT in osteomyelitis.

Discussion

Very little evidence is available on the use of HBOT for promoting fracture healing, or treating bone avascular necrosis or osteomyelitis. Controlled trials following the recommendations given in the Cochrane review\textsuperscript{135} should be undertaken to inform on these indications. Currently there is insufficient evidence to support routine use of HBOT in the treatment of these conditions.
### Table 4.12-1 Evidence on using HBOT for orthopaedic indications - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett <em>et al</em>., 2005</td>
<td>Systematic review</td>
<td>To assess the evidence for the use of HBOT as an adjunctive therapy for treating actual or expected delayed or non-union bone fractures.</td>
<td>Comprehensive search of electronic databases, attempts to identify grey literature and hand searching.</td>
<td>Randomised or quasi-randomised trials in patients with bony fractures. Comparator was either standard care alone or placebo HBOT. All languages included. Search to 2003/4.</td>
<td>No studies met the inclusion criteria.</td>
<td>It is not possible to say whether HBOT is beneficial for the treatment of fractures. High quality clinical trials need to be undertaken.</td>
</tr>
<tr>
<td>Liu <em>et al</em>., 2003</td>
<td>HTA</td>
<td>To assess whether HBOT is beneficial in the treatment of avascular necrosis of bone.</td>
<td>Comprehensive search of electronic databases, bibliography scanning and attempts to identify grey literature. Search conducted Nov 2003.</td>
<td>Included secondary literature, comparative or observational studies. English language studies only. Observational studies: Scherer <em>et al</em>., 2000, Reis <em>et al</em>., 2003.</td>
<td>Scherer <em>et al</em>. Study conducted in paediatric population and so was not appropriate for current review. Reis <em>et al</em>. 12 adults with 16 avascular necroses of hip bone. Inclusion criteria - Steinberg stage 1 and MRI lesion ≥4mm thick and/or ≥12.5mm long. 2 cases of steroid induced and 14 were idiopathic. <strong>Intervention:</strong> HBOT versus no control group. Outcomes compared indirectly with Vande Berg <em>et al</em>., 1999.</td>
<td>There is insufficient evidence to support the effectiveness of HBOT in avascular necrosis. The one relevant study lacked a control group, was small, and did not provide baseline data. Both steroid related cases worsened.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/ characteristics</td>
<td>Inclusion/exclusion criteria</td>
<td>Results</td>
<td>Conclusions and comments</td>
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<tr>
<td>Lawson, 2003</td>
<td>Evidence review</td>
<td>To summarise the best available evidence on the effects of HBOT in patients with osteomyelitis.</td>
<td>Comprehensive search of electronic databases and reference list scanning.</td>
<td>Systematic reviews and controlled studies of patients with osteomyelitis treated with HBOT alone or adjunctive HBOT compared with any other treatment regimen and reporting clinical outcomes (signs, symptoms, function, disability, complications of osteomyelitis, adverse effects). Language restrictions unclear. Exclusion criteria: case series with &lt;30 participants.</td>
<td>2 systematic reviews described a single non-randomised trial (Esterhai, 1987) that was small and of poor quality. No significant difference in success rate (11 of 14 versus 13 of 14; p=0.28) or recurrence of infection (2 of 14 versus 1 of 14; p=0.54). Mean length of hospital stay was 54 days in the HBOT group and 47 days in the control group (no p-value).</td>
<td>There is insufficient evidence to assess the safety and efficacy of HBOT in osteomyelitis.</td>
</tr>
<tr>
<td>Wang et al., 2003</td>
<td>Systematic review</td>
<td>To determine whether adjunctive HBOT is effective for hypoxic wounds (only osteomyelitis considered here).</td>
<td>Existing systematic reviews were identified and the literature was updated by a MEDLINE search for articles published from mid 1998–August 2001, with expert opinion.</td>
<td>Published articles with at least 5 subjects, evaluating the use of HBOT for wound care and reporting clinical outcomes. RCTs, controlled trials and case series were included. Conference reports without primary data, animal studies and review articles were excluded.</td>
<td>1 controlled trial (Esterhai, 1987) and 1 case series. The controlled trial showed no significant effect of HBOT on healing outcomes.</td>
<td>No conclusions on the use of HBOT in osteomyelitis were drawn.</td>
</tr>
</tbody>
</table>
| Study Type | Medical Services Advisory Committee 2001
| Study Aim | To evaluate HBOT safety and effectiveness during treatment of various conditions (only osteomyelitis was assessed here).
| Search strategy/characteristics | Electronic database search, attempts to identify grey literature, expert opinion and reference list scanning.
| Inclusion/exclusion criteria | Included studies of HBOT in mono- or multiplace chambers, with a control group.
| Results | 1 controlled trial (Esterhai, 1987).
| Conclusion and comments | The HBOT regimen did not appear beneficial in patients with osteomyelitis. The generalisability of the study findings was questioned.
4.13 Surgery

Evidence identified

The available evidence comprised: one RCT that measured neutrophil activation following hepatectomy \(^{139}\); a retrospective case series without matched controls \((n=9)\) of HBOT for complications of lung transplantation \(^{140}\); two case reports of HBOT for complications following liver transplantation \(^{141}\); and a single case report of HBOT in postoperative care following penile replantation \(^{142}\). The studies informing on the use of HBOT in surgery are described in Table 4.13-1.

Evidence quality

The small RCT reported only surrogate outcomes, the method of randomisation was not reported and the study was not blinded \(^{139}\). The remaining evidence was weak with a high likelihood of study and publication bias.

Results

The RCT reported reduced and delayed levels of polymorphonuclear leukocyte elastane and thrombomodulin and suppressed elevation of CD18 expression in 12 patients treated with HBOT versus 12 controls \(^{139}\).

A retrospective study reported outcomes for nine patients who received HBOT \((1–25\) treatments at \(100\%\) FiO\(_2\), \(100–180\) kPa, \(100\) minutes per session\) for osteomyelitis \((n=4)\), cellulitis \((n=2)\), septic arthritis \((n=1)\), ischaemic toes \((n=1)\) or cerebral arterial gas embolism \((n=1)\) following lung transplantation \(^{140}\). One patient died without improvement, two had HBOT stopped (without improvement) because of barotrauma \((n=1)\) or seizure \((n=1)\) and the others improved slightly or significantly.

All three case reports noted successful outcomes and no adverse effects \(^{141,142}\).

Discussion

There is currently insufficient evidence to support the routine use of HBOT in the treatment of surgical patients.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ueno et al., 1999</td>
<td>RCT</td>
<td>To investigate HBOT on post-operative sinusoidal endothelial cell damage by activated neutrophils.</td>
<td>12 patients given HBOT 2.0 ATA for 60 minutes at 3 and 24 hours post surgery. 12 control patients treated to maintain normal haemodynamic values.</td>
<td>Non-cirrhotic patients undergoing elective hepatectomy for liver cancer.</td>
<td>Statistically significant differences in polymorphonuclear leukocyte elastase and thrombomodulin concentrations were observed at 12 and at 12 and 48 hours post-operatively respectively. Levels of CD18 were suppressed in patients treated with HBOT compared to controls.</td>
<td>Only surrogate outcomes were reported. Method of randomisation was not described. No reporting of blinding of study.</td>
</tr>
<tr>
<td>Higuchi et al., 2006</td>
<td>Retrospective case series</td>
<td>To evaluate the efficacy and safety of HBOT for complications following lung transplantation.</td>
<td>9 patients with osteomyelitis (n=4), cellulitis (n=2), septic arthritis (n=1), ischaemic toes (n=1) or cerebral arterial gas embolism (n=1) following lung transplantation. HBOT: 1–25 treatments at 100% FIO2, 100–180 kPa, 100 minutes/session. Control: none. Outcomes: reponse of post-operative complications to HBOT.</td>
<td>Lung transplantation patients who underwent HBOT as identified in the database of the hospital hyperbaric unit.</td>
<td>One patient died without improvement, two had HBOT stopped (without improvement) because of barotrauma (n=1) or seizure (n=1) and the others improved slightly or significantly.</td>
<td>HBOT is safe and appeared useful in the management of infectious complications in particular. The study design has a high likelihood of bias.</td>
</tr>
</tbody>
</table>
4.13.1 Cardiopulmonary bypass

A single RCT assessed the effect of HBOT on neuropsychometric dysfunction and inflammatory response following cardiopulmonary bypass as is summarised in Table 4.13-2. The trial was summarised in a previous technology assessment. The trial authors concluded that pretreatment with HBOT seemed to modulate the inflammatory response and reduce neuropsychometric dysfunction after bypass surgery but that multicentre RCTs are needed to confirm these findings.
Alex et al., 2005. RCT
To evaluate HBOT in patients undergoing cardiopulmonary bypass.
64 adults (mean age 66 years) scheduled to undergo coronary revascularisation.
HBOT: 100% O2, 2.4 ATA, 3 sessions at 24, 12 and 4h before surgery.
Control: air, 1.5 ATA, with the same regimen as the HBOT group.
Outcomes: laboratory analysis of inflammatory response and neuropsychometric assessment.
Exclusion criteria: emergency operation, >80 years, poor English, learning difficulties, visual or hearing impairment, claustrophobia, history of cerebrovascular disease, pneumothorax or middle ear disease or immunosuppressive or steroid therapy.
The control group had a significant postoperative increase in some inflammatory response markers that was not observed in the HBOT group. The proportion of patients with neuropsychometric dysfunction was higher in the control group (p=0.05).
The results indicated that HBOT pretreatment can modulate the inflammatory response and reduce neuropsychometric dysfunction.
4.14 Urology

Evidence identified

A double-blind RCT compared HBOT with a sham intervention in women with interstitial cystitis\textsuperscript{144}. The only other data identified comprised three case reports of HBOT for cystitis, which are not described here and the study of haemorrhagic post-radiotherapy cystitis which is included in Section 4.9. The studies informing on the use of HBOT to treat urological indications are described in Table 4.14-1.

Evidence quality

The RCT did not report any details of the randomisation method and provided no indication of adequate allocation concealment to reduce the likelihood of bias\textsuperscript{144}. Patients and investigators (except the statistician) were blinded up to the 3-month follow up (only HBOT responders were followed up further). All outcomes were patient reported. The sample size (n=21) had no statistical basis, rather the investigators considered this sufficient to provide some indication of whether HBOT had any effect on symptoms. Analysis was performed on an intention-to-treat basis, i.e., the 2 patients who withdrew were included.

Results

The RCT showed no statistically significant difference in the primary measure of treatment response (moderate or marked improvement on Global Response Assessment) between HBOT and sham treatment in women with interstitial cystitis at the 3-month follow up\textsuperscript{144,145,146}. Secondary outcome analysis found a statistically significant difference in change in pain symptoms from baseline at 3 months in favour of HBOT. In the absence of an effect on the primary outcome this finding should be interpreted with caution. Satisfaction with treatment outcome was rated as poor by 5 of 12 patients who completed HBOT and all 7 patients in the control group.

One patient dropped out of the HBOT group because of mild oxygen intoxication. One HBOT patient suffered transient hearing impairment whilst in the chamber and four reported problems with visual accommodation during treatment. At the start of the study one patient was given medication to control claustrophobia. One patient in the HBOT group failed to complete the study due to poor attendance\textsuperscript{144}.

Discussion

Data from one small RCT provides little evidence of benefit for HBOT in women with interstitial cystitis\textsuperscript{144} and therefore it should not currently be used in the routine treatment of patients with this condition although data from future RCTs may provide more evidence in this respect.
van Ophoven et al., 2006

**Type:** RCT  
**Aim:** To evaluate the safety, efficacy and feasibility of HBOT for interstitial cystitis.  
**Search strategy/characteristics:**  
- **Inclusion/exclusion criteria:**  
  - Interstitial cystitis
  - National Institute of Diabetes and Digestive and Kidney Diseases diagnostic criteria.

**Results:**  
- There was no statistically significant difference between groups in moderate or marked improvement on GRA at 3-month follow up.  
- There was a statistically significant difference in the mean change in pain symptoms from baseline at 3 months in favour of HBOT (43.1±20.5 versus 31.2±19.8; p<0.05).  
- 1 HBOT patient dropped out because of mild oxygen intoxication, 1 suffered transient hearing impairment whilst in the chamber and 4 reported problems with visual accommodation.

**Conclusions and comments:**  
HBOT appeared safe and effective. In the absence of any description of the randomisation procedure, no apparent protection against selection bias, a sample size with no statistical basis and only 1 secondary outcome reaching statistical significance, the authors' conclusion is questionable.

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**Table 4.14-1 Evidence on using HBOT to treat interstitial cystitis - included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Ophoven et al., 2006</td>
<td>RCT</td>
<td>To evaluate the safety, efficacy and feasibility of HBOT for interstitial cystitis.</td>
<td>21 women (42–78 years) with interstitial cystitis. HBOT: 100% O₂, 2.4 ATA, 90 min daily 6 times/week over 5 weeks (30 sessions). Control: sham treatment, air, 1.3–1.4 ATA, 90 min daily 6 times/week over 5 weeks (30 sessions).</td>
<td>Interstitial cystitis National Institute of Diabetes and Digestive and Kidney Diseases diagnostic criteria.</td>
<td>There was no statistically significant difference between groups in moderate or marked improvement on GRA at 3-month follow up. There was a statistically significant difference in the mean change in pain symptoms from baseline at 3 months in favour of HBOT (43.1±20.5 versus 31.2±19.8; p&lt;0.05). 1 HBOT patient dropped out because of mild oxygen intoxication, 1 suffered transient hearing impairment whilst in the chamber and 4 reported problems with visual accommodation.</td>
<td>HBOT appeared safe and effective. In the absence of any description of the randomisation procedure, no apparent protection against selection bias, a sample size with no statistical basis and only 1 secondary outcome reaching statistical significance, the authors' conclusion is questionable.</td>
</tr>
</tbody>
</table>
4.15 Headache

Migraine headaches are relatively common, affecting up to 15% of the population in Europe and North America, and are thought to be one of the commonest reasons for seeking medical help147. Triptans became available for the treatment of migraine in the 1990s and their effectiveness has made them the therapy of choice of patients, although a proportion of patients experience intractable migraine.

Cluster headaches are less common occurring in around 0.2% of the population148. They are distinguished by their severity and occur daily for up to several weeks before resolving. Standard treatment for cluster headache is sumatriptan and inhalation of 100% oxygen148.

Both migraine and cluster headache have been treated with HBOT for some time, with the suggested mode of action being the induction of metabolic changes and vasoconstriction10.

4.15.1 Migraine

Evidence identified

A double-blind RCT compared HBOT with air placebo to assess prophylactic effects on migraine149. A systematic review undertaken for HTA in Australia described two earlier RCTs, one a crossover study, that assessed acute effects on migraine comparing HBOT with normobaric oxygen sham procedures8. The three RCTs were published from 1995–2004. A Cochrane review is currently under development148. The studies informing on the use of HBOT to treat migraine are described in Table 4.15-1.

Evidence quality

None of the RCTs reported sufficient information to assess the adequacy of randomisation and allocation concealment was unclear in all three trials. Two trials, including the crossover study, were double-blind. The number of participants in each trial ranged from 8–34 and each trial used different subjective outcomes to measure the effect. The systematic review reported no losses to follow up in the earlier trials5, whereas in the most recent trial 6 of 40 participants did not complete the study (the treatment group was not reported)149. The systematic review did not report whether analysis of the crossover trial was appropriate to the study design but inspection of the original paper revealed that the method of analysis was not appropriate for paired data and did not include analysis of order, period or period-treatment effect150.

Results

The most recent and largest of the trials (n=34) found no statistically significant difference in the mean change in hours of headache/week pre- and post-treatment, comparing HBOT and placebo. There was no significant difference in the dose of attack-averting drugs required or in blood endothelin-1 levels149.

A crossover trial involving 8 women who had migraine with aura found a significantly greater improvement in headache severity measured on a VAS when HBOT was administered within 2 hours of onset, compared with a sham procedure using normobaric oxygen. Pain measured by palpation or dolorimetry showed no difference between treatment and control groups8. The results were based on a simple treatment comparison (pre-treatment versus post-treatment results in each group) which was inappropriate to the crossover study design. The parallel group RCT in adults with a history of migraine using a different VAS, found that 9 of 10 patients indicated ‘none’ or ‘mild’ pain after HBOT compared with 1 of 10 who received the normobaric oxygen sham procedure8.

No data were reported on adverse effects. Two patients who withdrew from one trial did so because of claustrophobia149.

Discussion

Controlled trial data have failed to show a significant prophylactic effect for HBOT on migraine. Although there is some evidence that HBOT provides pain relief, the reliability of the findings is uncertain because randomisation procedures were not adequately described, trials included small numbers of participants and used heterogeneous subjective measures of effect. Therefore, there is insufficient evidence to support the routine use of HBOT for patients with migraine.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Services Advisory Committee 2000</td>
<td>HTA</td>
<td>To evaluate HBOT safety and efficacy in treating a number of conditions</td>
<td>Comprehensive electronic database search, attempts to identify grey literature, expert opinion and reference list scanning. Covered literature from 1966–1999. Quality assessment based on NHMRC revised evidence hierarchy.</td>
<td>English language only. Trials with a control group.</td>
<td>2 small RCTs were identified. Both studies compared HBOT with sham treatment. Both studies reported statistically significant differences in responses to a visual analogue scale of severity of headache favouring HBOT over sham treatment.</td>
<td>Method of randomisation was unclear for both studies and one study used single masking only.</td>
</tr>
<tr>
<td>Eltedal et al., 2004</td>
<td>RCT</td>
<td>To determine the prophylactic effect of HBOT on migraine sufferers with frequent attacks.</td>
<td>40 adults (21–65 years) with migraine with or without aura. HBOT: 100% O₂, 2 ATA, 30 min, 3 sessions over 3 consecutive days. Control: placebo air, 2 ATA, 30 min, 3 sessions over 3 consecutive days. Patient diary records of number of headache attacks, whether migraine or not, duration, intensity, other symptoms and doses of attack averting drugs; diary kept for 8 weeks before and after treatment. Primary outcome: difference in hours of headache/week pre- and post-treatment. Secondary outcomes: days of headache/week, doses of attack averting drugs/week and blood endothelin-1 levels.</td>
<td>Migraine by International Headache Society criteria and 2–8 attacks/month in the last 3 months. Exclusion criteria: serious claustrophobia, history of lung injury or serious lung disease.</td>
<td>There was no statistically significant difference in the mean change in hours of headache/week pre- or post-treatment between HBOT and placebo. There was no significant difference in the doses of attack-averting drugs used or blood endothelin-1 levels.</td>
<td>HBOT had no significant prophylactic effect on migraine or blood endothelin-1 levels. The method of randomisation was not reported and 6 of 40 randomised participants did not complete the study.</td>
</tr>
</tbody>
</table>
4.15.2 Cluster headache

Evidence identified

A placebo-controlled double-blind crossover RCT published in 2002 used information on the number, duration and severity of attacks, as recorded in patient diaries to compare HBOT with placebo (sham treatment) in patients with chronic or episodic active cluster headache. An earlier systematic review undertaken for an HTA in Australia described two non-randomised comparative studies published in 1996 and 1997. One compared patients with chronic cluster headache and the other compared patients with episodic cluster headache versus concurrent controls. A Cochrane review considering treatment of cluster headaches is currently under development. The studies informing on the use of HBOT to treat cluster headache are described in Table 4.15-2.

Evidence quality

In the crossover RCT the method of randomisation to treatment order was not described, the sample size was not justified and the analysis was poorly reported, raising concern about the reliability of the results. The authors acknowledged that selection of patients with long cluster periods could have influenced the results.

The literature search conducted for the systematic review was sufficiently extensive to identify relevant studies up to 1999. Inclusion was restricted to studies published in English, therefore, the possibility of publication and language bias cannot be ruled out. The included studies used concurrent controls but were not randomised.

Results

The crossover RCT included 16 patients. Two episodic patients became free of symptoms for more than a year after receiving only placebo and consequently did not crossover to receive HBOT. The study did not show a statistically significant difference in effectiveness between two HBOT sessions 24 hours apart and placebo. Assessment used >50% reduction in the headache index (HI) 1 week after treatment compared with 1 week before treatment to define efficacy (HI = the sum of [the number of attacks x degree of severity]). A similar proportion of patients responded to placebo (6 of 12 episodic, 0 of 4 chronic) as to HBOT (4 of 10 episodic, 1 of 4 chronic). No patients responded to both treatments and 5 did not respond to either treatment. There was no systematic difference in blood levels of neuropeptides, endothelium or nitrate comparing treatment and control groups, and responders with non-responders.

The two non-randomised studies described in the systematic review included a total of 28 participants. One study of chronic cluster headache reported a reduction in the mean number of attacks among 10 patients who received HBOT (30 minutes every two days for 15 sessions) compared with 4 patients who received normobaric air according to the same schedule. The study reported graphical rather than numerical data. A smaller study of episodic cluster headache found a significant decrease in the mean density score for substance P immunoreactivity in patients given HBOT (n=7) compared with normobaric air (n=7). The relationship of this effect to clinical outcome was unclear. No adverse effects data were reported.

Discussion

There is insufficient evidence that HBOT is an effective treatment for cluster headache. The one RCT included only 16 patients and found no evidence that HBOT is more effective than placebo at interrupting the period of active cluster headache. The findings from other comparative studies were considered unreliable due to methodological limitations and poor reporting.
### Table 4.15-2 Evidence on using HBOT to treat cluster headache - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
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</tr>
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<tbody>
<tr>
<td>Medical Services Advisory Committee 2000⁴</td>
<td>HTA</td>
<td>To evaluate HBOT safety and efficacy in treating a number of conditions</td>
<td>Comprehensive electronic database search, attempts to identify grey literature, expert opinion and reference list scanning. Covered literature from 1966–1999. Quality assessment based on NHMRC revised evidence hierarchy.</td>
<td>English language only. Trials with a control group.</td>
<td>2 small controlled studies from the same institute were identified. A reduction in mean number of attacks among 10 patients who received HBOT (30 minutes every 2 days for 1.5 sessions) compared to 4 patients who received NBOT. The second study measured a surrogate endpoint, the immunoreactivity of substance P and found the mean density score was decreased in the HBOT group (n=7) compared with controls (n=4).</td>
<td>The groups were not randomised, one study was not masked, the other single masked. The significance of the surrogate end point was not clear.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/characteristics</td>
<td>Inclusion/exclusion criteria</td>
<td>Results</td>
<td>Conclusions and comments</td>
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<tr>
<td>Nilsson Remahl et al., 2002</td>
<td>Crossover RCT</td>
<td>To determine if HBOT is more effective than sham treatment for active cluster headache.</td>
<td>16 adults (20–62 years) with episodic (n=12) or chronic (n=4) cluster headaches. HBOT: 100% O₂ in a hyperbaric chamber, 250 kPa for 70 min, 2 sessions 24h apart. Control: placebo 10% O₂ in nitrogen, in a hyperbaric chamber, 250 kPa for 70 min, 2 sessions 24h apart. If intervention was effective crossover was postponed until the patient fulfilled the inclusion criteria again, otherwise the alternative intervention was given 1 week later. Patient diary record of number of attacks, duration and severity (VAS). Headache Index calculated as sum of (number of attacks x degree of severity) 1 week prior to and 1 week after treatment. Effective treatment defined as &gt;50% reduction in HI. Blood neuropeptides, endothelins and nitrate levels.</td>
<td>Chronic or episodic active cluster headache. Cluster period ≥ 6 attacks within 1 week pretreatment and an expected remaining headache period of &gt;4 weeks. Exclusion criteria: using prophylactic treatment, cardiovascular problems, history of ear disorders, pregnant or nursing.</td>
<td>There was no statistically significant difference in HI (1 week after treatment relative to 1 week before treatment) between HBOT and placebo. There was no difference in blood neuropeptides, endothelins or nitrate between HBOT and placebo or between responders and non-responders.</td>
<td>HBOT was not more effective than placebo in reducing HI or interrupting the cluster period. The method of randomisation to treatment order was not described, the sample size was not justified and the analysis was poorly reported.</td>
</tr>
</tbody>
</table>


4.16 Hearing disorders

Sudden hearing loss is relatively common with 5–20 cases per 100,000 of the population but there is little consensus regarding appropriate treatment strategies. Although the treatment of choice for many practitioners is systemic steroids, alternatives such as antiviral agents and mineral, vitamin and herbal preparations have also been used. High rates of spontaneous recovery and inadequate study design have resulted in continuing controversy regarding optimal care for this group of patients.

Treatments for tinnitus, the most common hearing disorder, have predominantly been directed at the impact of the condition on quality of life and have included use of antidepressants, benzodiazepines or masking devices. However herbal remedies, acupuncture and placebo treatments have also been used.

Hyperbaric oxygen has been used as a treatment for hearing disorders since the 1960s on the basis that the impairment may result from hypoxia within the cochlea and that the oxygen partial pressure in the perilymph of the inner ear rises with hyperbaric oxygen treatment.

Evidence identified

The AHRQ report identified two HTAs. The search conducted for this report also identified a Cochrane review, a systematic review and an RCT comparing two HBOT regimens. A paper including the results of the systematic review, conducted as per the Cochrane review and published by the same authors was also identified but as it contained the same information was not subjected to data extraction. In addition, the literature search identified a number of cohort and case studies and narrative reviews from which data were not extracted. Details of included studies are presented in Table 4.16.1.

Evidence quality

The AETMIS report searched a limited number of databases and identified only one evidence source, a narrative review of studies of hyperbaric oxygen as primary or adjunctive therapy.

The MSAC report of 2001 was a wide-ranging review of HBOT for a number of indications, including sudden deafness and acoustic trauma. The authors identified four comparative studies all published in the mid-1990s, three of which were described as RCTs (although this did not concur with the data given in evidence tables).

The Cochrane review was a well-conducted report of a systematic search of a large number of databases, to identify controlled trials of HBOT for idiopathic sudden sensorineural hearing loss and tinnitus. The review identified six controlled trials published from 1995–2004 that met the inclusion criteria.

Conlin and Parnes undertook a limited search of studies for sensorineural hearing loss and identified only one using HBOT; this trial was also identified by the Cochrane review.

One additional RCT was identified by the search of recent primary literature conducted for this report, and comprised a trial of hyperbaric oxygen for the alleviation of tinnitus. The randomisation process used was unclear, the report did not indicate an attempt to ensure allocation concealment and blind participants to their treatment, and there was no indication of the relative similarities or differences between participants in each treatment group.

The two cohort studies, one prospective and one retrospective, were subject to a number of potential biases including subject selection, variation in medical treatment for those receiving and not receiving HBOT, timing of audiological assessment, and differences in baseline characteristics.

Results

Both HTAs concluded that studies conducted to date have been insufficiently rigorous to provide convincing evidence of the effectiveness of HBOT in the treatment of hearing disorders.

The Cochrane review indicated that, on pooling results from two studies, there was a significantly higher chance of a 25% improvement in the pure tone average (PTA) measure of hearing loss when HBOT was used. There was also a 22% greater chance of hearing improvement with HBOT. Poor reporting resulted in no discernable difference in a subjective measure of tinnitus following HBOT. The authors concluded that HBOT significantly improved hearing loss but the clinical significance of the difference was not clear and that routine use of HBOT for this patient group could not be recommended.

The second systematic review reported on one trial that was included in the Cochrane review.

The recent trial of two HBOT protocols for tinnitus identified no significant difference in subjective symptom assessment but did identify a significant difference in outcomes amongst those who indicated positive or negative expectations of treatment. The authors concluded that psychological mechanisms influence the therapeutic effect of HBOT.

Discussion

The evidence base for the use of HBOT in the treatment of hearing disorders is small and includes very few rigorously conducted and adequately reported primary studies. The early literature comprised mainly cohort studies many of which were compromised by poor patient selection procedures, variations in HBOT protocols and comparator therapies and differences in the nature and timing of audiological assessments. However more recent literature had similar limitations. A number of RCTs have been carried out and these formed the basis of a Cochrane review, which concluded that HBOT did improve hearing loss but that the clinical significance of the improvement was unclear. Further large scale RCTs which consider patient focussed outcomes may provide more useful information.
Lamm et al. noted that 65% of patients with hearing loss spontaneously recover either completely or to a large degree, but go on to recommend adjunctive HBOT for cases where conventional treatment is unsuccessful. However, there is no standard therapy of proven effectiveness for patients with hearing loss. In the absence of evidence of a beneficial effect, HBOT cannot be recommended as a treatment for hearing disorders.
### Table 4.16-1 Evidence on using HBOT to treat hearing disorders - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
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</thead>
<tbody>
<tr>
<td>Medical Services Advisory Committee, 2001*</td>
<td>HTA</td>
<td>To evaluate the safety and effectiveness of HBOT for a range of conditions.</td>
<td>A systematic review of the literature from 1966–1999 using a number of OVID databases, Cochrane database, HealthSTAR and National Guidelines Clearing House and HTA group websites.</td>
<td>Articles were excluded if they considered a pre-agreed condition, were uncontrolled, did not have a comparator group or were not published in English.</td>
<td>4 studies (3 RCTs) of sudden deafness or acoustic trauma were identified. The adequacy of randomisation could not be determined and the studies were poorly described. The degree of heterogeneity, particularly in comparator therapy, meant that results could not be pooled. Study findings conflicted and only one study reported statistically significant hearing improvements.</td>
<td>The use of HBOT in the treatment of hearing loss is not supported by the evidence.</td>
</tr>
<tr>
<td>Bennett et al., 2007†</td>
<td>Systematic review (Cochrane)</td>
<td>To assess the effectiveness of HBOT in treatment of idiopathic sudden sensorineural hearing loss and tinnitus.</td>
<td>Search to June 2006 in Cochrane library, MEDLINE, EMBASE, CINAHL, AMED, LILACS, KOREAMED, INDMED, the National Research Register, CSA, ISI proceedings and ZETOC.</td>
<td>RCTs and pseudo-RCTs of acute or chronic idiopathic sensorineural hearing loss and/or tinnitus where HBOT was used as treatment.</td>
<td>Of 91 publications, 6 trials were included in the review. There was no statistically significant difference in the main outcome (proportion of subjects with greater than 50% hearing improvement) between control and intervention groups. Pooled data from 2 trials gave an RR of 1.53 (95% CI: 0.85, 2.78; p=0.16).</td>
<td>There is no justification for the use of HBOT among this group of patients. 3 trials (Cavallazzi et al., 1996; Fattori et al., 2001; Hoffman et al., 1995) had insufficient power to detect a clinically significant difference between groups for the main outcome. Trials were methodologically poor and the clinical importance of the observed &gt;25% improvement in hearing loss is unclear.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/ characteristics</td>
<td>Inclusion/exclusion criteria</td>
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<tr>
<td>Conlin &amp; Parnes, 2007</td>
<td>Systematic review</td>
<td>To review the literature on effectiveness of treatments for sudden sensorineural hearing loss and provide estimates of the efficacy of individual treatments.</td>
<td>MEDLINE search for RCTs published in English from Jan 1966–Feb 2006 and hand searching of original articles and reviews.</td>
<td>Studies comparing treatment and control groups in patients with sudden sensorineural hearing loss, idiopathic sudden sensorineural hearing loss or sudden deafness.</td>
<td>20 RCTs met the inclusion criteria, 1 used HBOT (Topuz et al., 2004). This trial reported statistically significant greater hearing gain in the HBOT group.</td>
<td>The HBOT trial was of limited methodological quality. The limited search strategy accounts for the identification of only 1 trial using HBOT.</td>
</tr>
<tr>
<td>Porubsky et al., 2007</td>
<td>RCT of 2 HBOT protocols.</td>
<td>To evaluate the effectiveness of HBOT in tinnitus with consideration of patients' pre-treatment expectations and the role of psychological factors.</td>
<td>360 patients with tinnitus were randomised to either 2.2 bar for 60 min or 2.5 bar for 60 min once/day for 15 days.</td>
<td>There was no difference between treatment protocols on tinnitus symptoms. There was no difference in effect of either treatment, between patients treated soon after symptom onset and those who had experienced symptoms for longer. A statistically significant correlation was noted between psychological factors and therapeutic effect.</td>
<td>Patient expectations influenced treatment when subjectively assessing HBOT efficacy. Randomisation method was not stated, allocation concealment was unclear. Approximately half of patients commenced treatment within 2 weeks of symptom onset. The remaining patients had delays from 2 weeks–1 year from symptom onset. Authors noted a high rate of spontaneous resolution of the condition within 2 weeks of onset.</td>
<td></td>
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</table>
4.17 Multiple sclerosis

Multiple sclerosis (MS) is a common neurological disease and 85% of patients have the relapsing-remitting form, which in most cases proceeds to the progressive phase. The causes of MS remain unknown but it may be an autoimmune condition with or without viral involvement. Acute attacks are treated with intravenous methylprednisolone for 3 days, and treatments to prevent or reduce the severity of relapses include interferons and glatiramer acetate.

The proposed mode of action of HBOT is unclear but it has been suggested that relief of focal hypoxia, suppression of macrophage activity and an increased level of endogenous steroids may be involved. HBOT shows beneficial effects in an animal model of MS, and case series studies have indicated effectiveness. A number of clinical trials have been undertaken to establish the efficacy of HBOT as a therapy for MS.

**Evidence identified**

A Cochrane systematic review of RCTs assessed the efficacy and safety of HBOT for the treatment of MS versus placebo or no treatment. The review included nine RCTs published from 1983–1990. The trials compared HBOT with various sham treatments. Several earlier reports based their assessment on this Cochrane review and/or a previous systematic review published in 1995.

Details of included studies are presented in Table 4.17-1. The following discussion is limited to the Cochrane review, which is the most up-to-date summary of the best available evidence.

**Evidence quality**

The Cochrane review used a comprehensive search strategy without language restriction. The last search date was June 2006. The review used explicit inclusion criteria and systematically assessed the quality of the included studies. Only two of the nine included trials reported adequate allocation concealment and most did not provide a clear description of the randomisation procedure. All trials reported blinding of participants and outcome assessors.

**Results**

The Cochrane review included a total of 504 participants in nine RCTs. The oxygen dose per session was 2.0 ATA for 90 minutes for most trials, and all used an initial course of 20 treatments over 4 weeks. All trials reported follow up at 1 month, seven trials at 6 months, and four trials at 1 year.

The primary outcomes of interest were improvement in disability using the Kurtzke Expanded Disability Status Scale (EDSS), MS exacerbations and side effects. Improvement in Kurtzke Functional Status Scores (FSS) was a secondary outcome.

Meta-analysis showed no statistically significant difference in the mean EDSS on completion of 20 treatments based on data from five RCTs (271 participants) or at 6 months follow up (three RCTs, 163 participants). At 12 months follow up pooled data from two RCTs (81 participants) showed a significant reduction in mean EDSS in favour of HBOT (WMD -0.85; 95% CI: -1.28, -0.42; p=0.0001).

There was no significant difference in the incidence of MS exacerbations during the initial 1-month treatment period (one RCT, 117 participants), at 6 months (two RCTs, 122 participants) or at 12 months follow up (two RCTs, 153 participants).

Meta-analysis of data from four RCTs (259 participants) showed a statistically significant increased risk of deterioration in visual acuity during HBOT (OR 24.87; 95% CI: 1.44, 428.50; p=0.03), although this was largely attributable to a very high event rate (55 of 60 participants) in the HBOT group in one trial compared with no events in the control group. Meta-analysis of six RCTs (349 participants) showed no significant difference in barotrauma episodes regardless of whether the sham treatment was at low or high pressure.

Analysis of secondary outcomes showed no significant difference in the number of participants who did not improve by at least one point in FSS on completion of 20 treatments or at 6 or 12 months follow up. Further analyses of individual elements of FSS found statistically significant effects in favour of HBOT for failure to improve pyramidal function at 6 and 12 months. However, the results were inconsistent between trials and the significant effect was largely attributable to data from one trial.

**Discussion**

A Cochrane review found no consistent evidence of benefit for HBOT as an MS treatment. The review was well conducted and the authors’ conclusions are likely to be reliable. The findings were consistent with an earlier high quality systematic review. Updated searches failed to identify RCTs published after the last search date in the Cochrane review.
Bennett & Heard, 2004

**Aim:** To evaluate the efficacy and safety of HBOT for the treatment of MS.

**Search strategy/characteristics:** Cochrane Multiple Sclerosis Group trials register, CENTRAL, MEDLINE, EMBASE, DORCTHIM, NLM, hand searching of hyperbaric journals, proceedings and extracts, reference lists and contacting trial authors.

**Inclusion/exclusion criteria:** RCTs in patients with MS, comparing HBOT with placebo or no treatment, that reported at least one outcome of interest were eligible for inclusion. There was no language restriction.

9 RCTs including 504 participants were included (Barnes, 1985; Barnes, 1987; Confavreux, 1986; Fischer, 1983; Harpur, 1986; L’Hermitte, 1986; Neiman, 1985; Oriani, 1990; Wiles, 1986; Wood, 1985). Most did not clearly describe the randomisation procedure. All reported blinding of participants and outcome assessors.

There was no statistically significant difference in mean EDSS on completion of treatment (5 RCTs, 271 participants) or at 6 months follow up (3 RCTs, 163 participants). At 12 months follow up pooled data from 2 RCTs (81 participants) showed a significant reduction in mean EDSS in favour of HBOT (WMD -0.85; 95% CI: -1.28; -0.42; p=0.0001).

There was no significant difference in MS exacerbations at 1, 6 or 12 months. Meta-analysis (4 RCTs, 259 participants) showed a significant increase in risk of deterioration of visual acuity during HBOT (OR 24.87; 95% CI: 1.44, 428.50; p=0.03) but no significant difference in the incidence of barotrauma (6 RCTs, 349 participants).

There was no consistent evidence to indicate a beneficial effect for HBOT in MS. The few isolated analyses suggestive of benefit need to be confirmed in well-designed trials.

### Table 4.17-1 Evidence on using HBOT to treat multiple sclerosis - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
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</thead>
<tbody>
<tr>
<td>Bennett &amp; Heard, 2004</td>
<td>Cochrane systematic review</td>
<td>To evaluate the efficacy and safety of HBOT for the treatment of MS.</td>
<td>Cochrane Multiple Sclerosis Group trials register, CENTRAL, MEDLINE, EMBASE, DORCTHIM, NLM, hand searching of hyperbaric journals, proceedings and extracts, reference lists and contacting trial authors.</td>
<td>RCTs in patients with MS, comparing HBOT with placebo or no treatment, that reported at least one outcome of interest were eligible for inclusion. There was no language restriction.</td>
<td>9 RCTs including 504 participants were included (Barnes, 1985; Barnes, 1987; Confavreux, 1986; Fischer, 1983; Harpur, 1986; L’Hermitte, 1986; Neiman, 1985; Oriani, 1990; Wiles, 1986; Wood, 1985). Most did not clearly describe the randomisation procedure. All reported blinding of participants and outcome assessors. There was no statistically significant difference in mean EDSS on completion of treatment (5 RCTs, 271 participants) or at 6 months follow up (3 RCTs, 163 participants). At 12 months follow up pooled data from 2 RCTs (81 participants) showed a significant reduction in mean EDSS in favour of HBOT (WMD -0.85; 95% CI: -1.28; -0.42; p=0.0001).</td>
<td>There was no consistent evidence to indicate a beneficial effect for HBOT in MS. The few isolated analyses suggestive of benefit need to be confirmed in well-designed trials.</td>
</tr>
</tbody>
</table>
4.18 Thermal burns

Introduction

It has been suggested that HBOT when used as an adjunct to standard burn care improves the healing of thermal burns by increasing oxygenation of the affected area.

Evidence identified

The literature search identified one recent Cochrane systematic review\textsuperscript{167}, a further systematic review\textsuperscript{168} and three HTAs\textsuperscript{8,10,11} relating to the use of HBOT for thermal burns. No additional trials since the last review were identified. Given the amount of secondary literature available no primary studies conducted prior to the date of the last review were considered. Studies informing on the use of HBOT to treat thermal burns are described in Table 4.18-1.

Evidence quality

The Cochrane review\textsuperscript{167} was considered of high quality. The authors made rigorous efforts to minimise bias by conducting a comprehensive systematic literature search, using clearly defined inclusion and exclusion criteria for assessing the validity of the results, and the results and conclusion were appropriate to the literature identified. The review by Saunders\textsuperscript{12} was also fairly well conducted, however limiting the analysis to papers in English resulted in some studies on this indication being excluded. The Quebec HTA\textsuperscript{10} suffered from some reporting inadequacies and was based on a fairly limited literature search, as was the Mitton and Hailey study\textsuperscript{11}. MSAC\textsuperscript{8} limited their search to English language papers but adopted a broader approach by including non-randomised controlled trials and RCTs. Despite the variations in the conduct of secondary studies, there was a high degree of overlap in component studies.

Results

The Cochrane review identified two RCTs relevant to this indication. Neither was considered of high methodological quality, with one being unblinded and the other including only a small number of patients. The studies varied substantially in their inclusion criteria, the nature of the comparator treatment and outcomes considered. As such, it was not possible for the review authors to statistically pool the results and the individual trials were considered separately. The authors noted that the larger (n=125) and more recent trial showed no significant difference in length of hospital stay, mortality or number of surgeries when comparing HBOT and control groups, after adjusting for patient conditions. The other trial (n=16) showed significantly shorter healing times for the HBOT group. On the basis of the evidence from the two trials, the Cochrane review concluded that while some promising results have been obtained using HBOT for thermal burns, there is insufficient evidence to support the use of HBOT for this indication.

The Quebec HTA\textsuperscript{10} and Mitton and Hailey\textsuperscript{11} were based on the same evidence as the Cochrane review but were considered less robust in their conduct. They are not discussed further here.

The Saunders review\textsuperscript{12} included one very small additional RCT that was excluded by the Cochrane review as the burns were experimentally induced and relatively minor. Saunders noted that this RCT showed a statistically significant reduction in hyperaemia (increased blood flow), exudation and wound size for the HBOT-treated group 2 days after injury, although this difference was not maintained in later days. This additional report added little to the evidence base, and Saunders also concluded that there is insufficient evidence to substantiate the use of HBOT for thermal burns.

The MSAC HTA\textsuperscript{8} adopted wider inclusion criteria, analysing five non-randomised controlled studies in addition to the three RCTs. As there were major differences in the study protocols, no statistical pooling of results was possible and results were presented narratively. The review noted that two studies of experimental burns showed significantly lower exudate volumes for the HBOT group, though the timing of this outcome varied between studies. The review also reported a statistically significant reduction in length of hospital stay based on one study, and a statistically significant reduction in healing time also based on one study. This evidence is susceptible to bias and does not add substantially to the information available from RCTs. The review authors concluded that there was little firm evidence to support the use of HBOT for thermal burns.

Discussion

Despite varying levels of robustness and differing study inclusion criteria, the overriding message from the secondary literature is that there is insufficient evidence to support the use of HBOT for treating thermal burns. While there appears to be some trend towards benefit for HBOT, these come from studies lacking in methodological rigour or use subjects with experimental burns. The RCT showing a benefit for HBOT was conducted over 20 years ago when burn care procedures were very different. Well-conducted RCTs are required to enable the few promising results to be verified. In the meantime the position on the use of HBOT for this indication remains unclear.
Table 4.18-1 Evidence on using HBOT to treat thermal burns - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
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</thead>
<tbody>
<tr>
<td>Villanueva et al., 2004[167]</td>
<td>Cochrane systematic review</td>
<td>To assess the evidence of HBOT benefit in the treatment of thermal burns.</td>
<td>Comprehensive search of electronic databases, reference list scanning, hand searching and expert opinion.</td>
<td>RCTs comparing the effect of HBOT versus no treatment or sham HBOT. Patients with thermal injuries to the epidermis, subcutaneous tissues, vessels, nerve, tendons or bone. Intervention: HBOT administered at pressures of 1.5–3 ATA for 30–120 minutes, at least once daily versus any standard treatment regimen. Outcomes: Primary: Mortality and major morbidity rate. Secondary: Acute fluid requirement, time to healing, requirement for grafts and/or debridement, length of hospital stay, scar quality, pain scores, activities of daily living and adverse effects.</td>
<td>2 RCTs (Brannen, 1997; Hart, 1974); statistical pooling of results was not possible. Brannen, 1997 (n=125) reported no difference in length of stay, mortality or number of surgeries between HBOT and control groups after adjusting for patient condition. Hart, 1974, (n=16) reported that mean healing times were significantly shorter in the HBOT group (mean: 19.7 days versus 43.8 days; p&lt;0.001). The relative risk of a failed graft without HBOT was 2 (95% CI: 0.5, 8). Fluid requirements were smaller in the HBOT group but no statistical analysis on this outcome was undertaken. 3 patients in the HBOT group experienced adverse events versus 1 patient in the control group.</td>
<td>While there are some promising results from 1 small RCT, there is insufficient evidence to support the routine use of HBOT for thermal burns. Methodological quality was rated as poor to very poor. The studies differed in outcomes and comparator treatment.</td>
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<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/characteristics</td>
<td>Inclusion/exclusion criteria</td>
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<td>Saunders, 2000</td>
<td>Systematic review</td>
<td>To determine whether HBOT is effective in the treatment of burns (other indications not considered here).</td>
<td>Comprehensive search of electronic databases, reference list scanning and expert opinion. Search from 1968 onwards.</td>
<td>RCTs in patients with thermal burns (no further detail provided). Intervention: HBOT (no further detail provided) versus unspecified comparator. Papers not in English were excluded.</td>
<td>3 RCTs (Brannen, 1997, n=125; Niezgoda, 1997, n=12; Hart, 1974, n=16). 2 RCTs (Niezgoda, 1997; Hart, 1974) reported significantly shorter healing time for the HBOT group, although the difference was short lived in one study.</td>
<td>There is insufficient evidence to recommend the use of HBOT in the treatment of thermal burns.</td>
</tr>
<tr>
<td>Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé, 2001</td>
<td>Technology assessment report</td>
<td>To determine the efficacy and safety of HBOT in the treatment of various conditions (thermal burns considered here).</td>
<td>MEDLINE search and reference list scanning. Literature in English and French available to 1999. Quality assessment undertaken but no details of method given.</td>
<td>Inclusion and exclusion criteria were not reported.</td>
<td>2 RCTs (Brannen, 1997; Niezgoda, 1997) A reduced healing time was seen in the Niezgoda RCT, with no significant difference in outcomes in the Brannen RCT.</td>
<td>There is sufficient evidence to support the use of HBOT in the treatment of severe burns which are refractory to treatment and/or compromise graft take.</td>
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<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/characteristics</td>
<td>Inclusion/exclusion criteria</td>
<td>Results</td>
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<tr>
<td>Medical Services Advisory Committee, 2001</td>
<td>HTA</td>
<td>To evaluate HBOT in terms of safety and effectiveness for the treatment of thermal burns (other indications not assessed here).</td>
<td>Comprehensive electronic database search, attempts to identify grey literature, expert opinion and reference list scanning. Covered literature from 1966–1999.</td>
<td>Included studies of HBOT in mono- or multiplace chambers, with a control group. Studies published in English.</td>
<td>3 RCTs (Brannen, 1997; Nezgoda, 1997; Hart, 1974) and 5 non-randomised controlled studies. 1 study showed less exudate in the HBOT groups, using experimental burns. No improvements in mortality were observed (four studies). Length of hospital stay was statistically significantly reduced in 1 study. Mean healing time was statistically significantly reduced in 1 study but no definition of healing was given. There is little firm evidence and a lack of well-conducted studies to support the use of HBOT therapy for thermal burns. There were differences in study populations and design, patient inclusion criteria and treatment protocols that precluded data pooling.</td>
<td></td>
</tr>
<tr>
<td>Mitton &amp; Hailey, 1998</td>
<td>HTA</td>
<td>To detail evidence on the effectiveness of HBOT to inform on establishing a second HBOT facility in Alberta (only efficacy of HBOT assessed here).</td>
<td>Limited literature search of electronic databases. Searched to 1997.</td>
<td>Included studies considered to be of the highest level of evidence for thermal burns.</td>
<td>2 RCTs (Brannen, 1997; Hart, 1974) and 1 controlled study. Results were contradictory with the largest and most recent RCT showing no evidence of benefit.</td>
<td>The evidence does not support the use of HBOT for thermal burns.</td>
</tr>
</tbody>
</table>
4.19 Miscellaneous uses

4.19.1 Sport injuries

The literature search identified a Cochrane systematic review of HBOT for delayed onset muscle soreness (DOMS) and closed soft-tissue injury as summarised in Table 4.19-1. This was summarised in a previous technology assessment conducted by AHRQ, which identified no additional RCTs. The Cochrane review concluded there was insufficient evidence to identify an effect for HBOT on ankle sprain, knee ligament injury or experimentally induced DOMS.
Raman et al., 2006

To assess the evidence for use of HBOT for adult sports injuries.

The Cochrane systematic review of HBOT for DOMS and closed soft-tissue injuries, including 9 RCTs (219 participants) was included. Meta-analysis of 7 trials of experimentally introduced DOMS showed significantly higher pain scores at 48 and 72h in the HBOT group (mean difference at 48h 0.88; 95% CI: 0.09, 1.67; p=0.03) but no difference in long-term pain, swelling or muscle strength. 1 trial in patients with ankle sprain found no difference in time to recovery, function, pain or swelling. 1 trial in patients with knee ligament injury found no difference in knee function.

There was insufficient evidence to establish the effectiveness of HBOT for acute injuries or DOMS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
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<th>Results</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Raman et al., 2006</td>
<td>Technology assessment report</td>
<td>To assess the evidence for use of HBOT for adult sports injuries.</td>
<td></td>
<td></td>
<td>The Cochrane systematic review of HBOT for DOMS and closed soft-tissue injuries, including 9 RCTs (219 participants) was included. Meta-analysis of 7 trials of experimentally introduced DOMS showed significantly higher pain scores at 48 and 72h in the HBOT group (mean difference at 48h 0.88; 95% CI: 0.09, 1.67; p=0.03) but no difference in long-term pain, swelling or muscle strength. 1 trial in patients with ankle sprain found no difference in time to recovery, function, pain or swelling. 1 trial in patients with knee ligament injury found no difference in knee function.</td>
<td>There was insufficient evidence to establish the effectiveness of HBOT for acute injuries or DOMS.</td>
</tr>
</tbody>
</table>
4.19 Miscellaneous uses

4.19.2 Dentistry

4.19.2.1 Osteonecrosis of the mandible

Bisphosphonate therapy is used to treat skeletal disorders such as bone metastases and osteoporosis. There is growing awareness that bisphosphonate therapy can cause osteonecrosis of the mandible whereby areas of jaw bone become exposed and necrotic\textsuperscript{170}. Understanding of the mechanisms leading to this complication is limited.

HBOT has been used in treatment and prevention protocols for osteonecrosis of the mandible, but given the uncertainties in the pathological processes involved use is still considered exploratory. Five case studies in which use of HBOT was discussed were identified by the literature search, but no higher level evidence was identified.

4.19.2.2 Periodontitis

The literature search identified a single Chinese RCT assessing the use of HBOT for severe periodontitis\textsuperscript{171} as summarised in Table 4.19-2. The trial was summarised in a previous technology assessment\textsuperscript{1}. Although the trial authors concluded that HBOT was beneficial, their findings were compromised by lack of reporting of randomisation methods and because subgroup analyses involved non-randomised comparisons.
<table>
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<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
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<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al., 2002&lt;sup&gt;171&lt;/sup&gt;</td>
<td>RCT</td>
<td>To assess HBOT as a treatment for periodontitis</td>
<td>24 patients (18–65 years) with severe periodontitis. HBOT: 100% O₂, 2.5 ATA, 90 mins per day. 10 sessions versus no HBOT. Outcomes: clinical (gingival indices, sulcus bleeding indices, probing depth, attachment loss), gingival blood flow and anaerobes.</td>
<td>Generalised severe periodontitis, pockets that could be probed to ≥4mm, approximately 25% loss of alveolar bone height (none had received irradiation in the past 3 years).</td>
<td>Left-sided teeth were treated with scaling and root planning. 4 groups compared HBOT, HBOT + scaling versus scaling alone and no treatment. Each showed statistically significant differences in clinical indices, probing depth, attachment loss, gingival blood flow and anaerobe counts in favour of HBOT (p&lt;0.01).</td>
<td>HBOT had beneficial therapeutic effects on severe periodontitis. However, the method of randomisation was not reported and the analysis methods were questionable.</td>
</tr>
</tbody>
</table>
4.19 Miscellaneous uses

4.19.3 Chronic hepatitis

The literature search identified a single RCT conducted in China assessing HBOT as a treatment for chronic hepatitis\textsuperscript{172} as summarised in Table 4.19-3. The trial was summarised in a previous technology assessment\textsuperscript{1}. The trial authors concluded that HBOT was effective but did not report sufficient information concerning the trial methods for the reliability of the findings to be determined.
Table 4.19-3  Evidence on using HBOT to treat chronic hepatitis - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
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</thead>
<tbody>
<tr>
<td>Liu et al., 2002</td>
<td>RCT</td>
<td>To assess the efficacy of HBOT for treating chronic hepatitis.</td>
<td>60 patients (20–60 years) with hepatitis B and/or C. HBOT: 100% O₂, 2.5 ATA, 2h per day for a total of 48 days versus medications manufactured in China. Outcomes: liver function tests, immunological tests, pathologic morphology and tissue HBV.</td>
<td>No criteria reported.</td>
<td>There was a significant decrease in serum liver enzyme levels and degeneration and necrosis of hepatocytes in the HBOT group (p&lt;0.05). Fibrosis and viral antigens were not significantly reduced.</td>
<td>HBOT was effective but could not reverse fibrosis or inhibit virus growth. The randomisation method was not reported.</td>
</tr>
</tbody>
</table>
4.19 Miscellaneous uses

4.19.4 Crohn’s disease

AHRQ¹ failed to identify any controlled studies of HBOT in patients with Crohn’s disease. An updated literature search identified a single case series of 10 patients with chronic severe perineal Crohn’s disease, which concluded that HBOT might be useful as a last resort treatment. The studies informing on the use of HBOT to treat Crohn’s are described in Table 4.19-4.
Table 4.19-4 Evidence on using HBOT to treat Crohn’s disease - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombel et al., 1995</td>
<td>Case series</td>
<td>To evaluate HBOT in patients with severe perineal Crohn’s disease.</td>
<td>10 patients with severe chronic perineal Crohn’s disease who had undergone surgical and one or more medical treatments without healing. HBOT: 100% O₂, 2.5 ATA, twice a day, 5 days a week (40 sessions), 2h per session. No controls. Outcome: cure.</td>
<td>Consecutive patients referred with severe perineal Crohn’s disease.</td>
<td>2 patients discontinued HBOT after a few sessions following eardrum perforation and bad psychological tolerance. 6 patients discontinued HBOT before completion of 40 sessions, 4 due to bad psychological tolerance and 2 because treatment was ineffective. 3 patients were cured completely and 3 partially.</td>
<td>HBOT might be useful as a last resort treatment for chronic perineal Crohn’s disease.</td>
</tr>
</tbody>
</table>
4.19 Miscellaneous uses

4.19.5 Bell's palsy

One RCT, conducted in Croatia, assessed the effectiveness of HBOT for moderate to severe Bell's palsy as summarised in Table 4.19-5. This trial was summarised in a previous technology assessment, which was subsequently used as the evidence source for the AHRQ technology assessment. The trial reported a significant difference in total recovery and average symptom duration in favour of HBOT. However, the method of randomisation was not described. The technology assessment concluded that the generalisability of the findings needs to be confirmed.
Table 4.19-5 Evidence on using HBOT to treat Bell's palsy - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racic et al., 1997</td>
<td>RCT</td>
<td>To compare the effects of HBOT versus prednisone in patients with Bell's palsy.</td>
<td>79 adults (13–77 years) with moderate to severe Bell's palsy. HBOT: 100% O₂, 2.8 ATA, for 1h twice a day, 5 days a week for a maximum of 30 sessions. Control: prednisone over 8 days and sham HBOT 7% O₂, 2.8 ATA, for 1h twice a day, 5 days a week for a maximum of 30 sessions. Outcomes: nerve excitability test before and after treatment, time to total recovery, complete recovery and palsy severity at 9 months follow up.</td>
<td>Diagnosis of Bell's palsy of less than 1 week duration, severity at least moderate. Exclusion criteria: contraindications (not specified).</td>
<td>Complete recovery was significantly greater in the HBOT group (37 of 40) compared with control (28 of 37; p=0.0122). The average time to recovery was significantly shorter in the HBOT group (22 days) compared with control (34 days; p&lt;0.001). At 9 months follow up 2 patients in the HBOT group had a positive nerve excitability test compared with 9 control patients (p&gt;0.05).</td>
<td>HBOT was more effective than prednisone in the treatment of Bell's palsy. However, the randomisation method was not described.</td>
</tr>
</tbody>
</table>
4.19.6 Pain syndromes

The literature search identified one controlled trial using HBOT to treat patients with complex regional pain syndrome (CRPS)\(^\text{175}\) and one controlled trial by the same investigators using HBOT to treat fibromyalgia\(^\text{176}\), as summarised in Table 4.19-6. These trials were summarised in a previous technology assessment\(^1\). The investigators concluded that HBOT was effective treatment for complex regional pain syndrome and had an important role in managing fibromyalgia. Although the trials were reported as RCTs\(^5\), treatment allocation was alternated and therefore non-randomised.
### Table 4.19-6 Evidence on using HBOT to treat pain syndromes - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiralp et al., 2004[^175]</td>
<td>Controlled trial</td>
<td>To assess the effectiveness of HBOT in CRPS.</td>
<td>71 patients (19–40 years) with post-traumatic CRPS.</td>
<td>Exclusion criteria: contraindications for HBOT.</td>
<td>Outcomes were significantly better in the HBOT group with the exception of wrist extension.</td>
<td>HBOT was well tolerated and effective at reducing pain and oedema and increasing range of motion.</td>
</tr>
<tr>
<td>Yildiz et al., 2004[^176]</td>
<td>Controlled trial</td>
<td>To evaluate the effect of HBOT in patients with fibromyalgia.</td>
<td>50 patients with fibromyalgia syndrome.</td>
<td>Fibromyalgia syndrome defined by American College of Rheumatology criteria, persistent symptoms despite medical and physical therapy.</td>
<td>There was a significant difference in all outcome measures in favour of HBOT except for pain scores after the first session (p=0.001).</td>
<td>The authors concluded that HBOT has an important role in managing fibromyalgia.</td>
</tr>
</tbody>
</table>
4.19 Miscellaneous uses

4.19.7 Cognitive impairment

A single RCT published in 1978 assessed the effect of HBOT in elderly patients with cognitive impairment as summarised in Table 4.19-7. The trial was summarised in a previous technology assessment. The trial authors concluded that the results did not support the view that either hyperbaric or normobaric oxygen had beneficial effects on cognitive impairment in the elderly.
Table 4.19-7 Evidence on using HBOT to treat cognitive impairment - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin et al., 1978</td>
<td>RCT</td>
<td>To evaluate the efficacy of HBOT and normobaric oxygen on cognitive impairment.</td>
<td>82 adults (62–85 years) with significant cognitive impairment. HBOT: 100% O₂, 2.5 ATA, 2 sessions of 90 min per day for 8 days. Controls: hyperbaric air; normobaric O₂; or normobaric air using the same regimen as for the HBOT group. Outcomes: psychological and psychophysical performance tests and symptom rating scales.</td>
<td>Ambulatory patients, 60–85 years, living in the community, with adequate intellectual function but with memory loss greater than expected for their age. Exclusion criteria: medical problems that would put the patient at risk on exposure to HBOT.</td>
<td>There was no significant difference in cognitive function or symptom reduction with normobaric O₂ or HBOT versus control patients who received normobaric or hyperbaric air.</td>
<td>The study failed to support the view that hyperbaric or normobaric oxygen has beneficial effects on cognitive impairment in the elderly. Double blinding in the trial was to O₂ or air, not to hyperbaric/normobaric conditions.</td>
</tr>
</tbody>
</table>
4.19.8 Eye disorders

The literature search identified three RCTs of HBOT for different eye disorders that were included in a previous technology assessment as summarised in Table 4.19-8. Detailed analysis of the studies showed that one trial clearly was not randomised and the reliability of randomisation in the other two trials was questionable. Statistical analyses were based on within-group changes in outcome measures before and after treatment, rather than differences between HBOT and control groups. A glaucoma trial found visual field improvement in HBOT subgroups (10, 20 or 30 sessions) for up to 3 months compared with no significant change in the hyperbaric placebo control group (30 sessions). There was no significant difference in visual acuity or intraocular pressure in any group. A trial in patients with keratoendotheliosis secondary to cataract surgery showed improved visual acuity with adjunctive HBOT compared with medication alone. A pilot study in patients with retinitis pigmentosa showed a significant increase in electroretinographic response in patients who received HBOT over 2 years and a significant decrease in the control group.

A rapid systematic review of HBOT for central retinal artery occlusion identified two retrospective case series that compared patients receiving adjunctive HBOT with comparators who received standard treatment. One study found statistically significant differences in visual acuity in favour of HBOT; the other observed similar effects in both groups. However, both studies had serious methodological weaknesses.
Raman et al., 2006

To assess evidence for HBOT as used in adult eye disorders.

3 RCTs considered: glaucoma (111 participants) [Boji et al., 1993], retinitis pigmentosa (48 participants) [Vingolo et al., 1999] and keratoendotheliosis (33 participants) [Recupero et al., 1992].

Boji et al., showed that HBOT improved visual field but not visual acuity or intraocular pressure in patients with glaucoma. Recupero et al., showed that adjunctive HBOT improved visual acuity in patients with keratoendotheliosis secondary to cataract surgery. Vingolo et al., showed that HBOT increased electroretinographic response in patients with retinitis pigmentosa.

The keratoendotheliosis trial was not an RCT, as patients considered at risk of adverse effects were allocated to the control group. The other two trials did not report the randomisation method. The results focused on analyses of within-group changes in outcome measures. The trials were poorly reported and the findings should be interpreted with caution.
4.19.9 Infertility

A poorly reported study which evaluated the effect of HBOT on endometrial development in women with infertility of unknown aetiology\textsuperscript{179} is summarised in Table 4.19-9. Although the abstract described the study as randomised no indication was given as to what or how randomisation was applied. The investigators used transvaginal doppler sonography to show significantly better endometrial quality in menstrual cycles when HBOT had been given.
Mitrović et al, 2006

**Study**

Mitrović et al, 2006

**Type**

RCT

**Aim**

To evaluate the effect of HBOT on endometrial development in women with infertility.

**Search strategy/characteristics**

32 women (24–34 years) with infertility of unknown aetiology. HBOT: 100% O₂, 2.3 ATA, 70 mins on 7 consecutive days from day 5 of the menstrual cycle over a 3-year period. Control: unclear, possibly cycles where HBOT was not applied. Outcomes: endometrial thickness and reflectivity, endometrial and uterine perfusion after HBOT.

**Inclusion/exclusion criteria**

Male infertility ruled out, no history of assisted reproductive techniques and using only moderate ovulation stimulants.

**Results**

Endometrial quality was significantly better in menstrual cycles when HBOT had been given (p<0.001).

**Conclusions and comments**

HBOT is the treatment of choice if endometrial receptivity is conditioned by adequate vascularisation and oxygenation. The study was poorly reported.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
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<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitrović et al, 2006</td>
<td>RCT</td>
<td>To evaluate the effect of HBOT on endometrial development in women with infertility.</td>
<td>32 women (24–34 years) with infertility of unknown aetiology. HBOT: 100% O₂, 2.3 ATA, 70 mins on 7 consecutive days from day 5 of the menstrual cycle over a 3-year period. Control: unclear, possibly cycles where HBOT was not applied. Outcomes: endometrial thickness and reflectivity, endometrial and uterine perfusion after HBOT.</td>
<td>Male infertility ruled out, no history of assisted reproductive techniques and using only moderate ovulation stimulants.</td>
<td>Endometrial quality was significantly better in menstrual cycles when HBOT had been given (p&lt;0.001).</td>
<td>HBOT is the treatment of choice if endometrial receptivity is conditioned by adequate vascularisation and oxygenation. The study was poorly reported.</td>
</tr>
</tbody>
</table>
4.19 Miscellaneous uses

4.19.10 Severe anaemia

Severe anaemia is an indication for which HBOT is approved by the Hyperbaric Oxygen Therapy Committee of the UHMS. A systematic review by van Meter examined the evidence for HBOT for severe anaemia, as summarised in Table 4.19-10. No details were given of the searches employed to identify the literature. The report identified nine studies considering HBOT in human subjects; all were case studies or case series with some patients also receiving transfusion. All studies noted a positive result using HBOT, but in the absence of a comparator group the effects of bias must be considered. However, HBOT may be particularly applicable to patients who cannot use blood products for religious reasons or because of transfusion incompatibility. The authors noted that there is also no RCT evidence supporting blood transfusion as a treatment of severe anaemia and that the potential for harm with blood transfusion is considerable. However, there remains no clear evidence to support the use of HBOT for severe anaemia.
Table 4.19-10 Evidence on using HBOT to treat severe anaemia - included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Meter, 2005¹⁸⁰</td>
<td>Systematic review</td>
<td>To review evidence for HBOT use to treat severe anaemia.</td>
<td>No search strategy details were provided.</td>
<td>No inclusion criteria were given.</td>
<td>9 case studies/series in human subjects reported positive results.</td>
<td>The evidence supporting HBOT use is not RCT based. However, RCT evidence does not exist for alternative interventions such as blood transfusion.</td>
</tr>
</tbody>
</table>
4.19 Miscellaneous uses

4.19.11 Malignant otitis externa

A Cochrane review of evidence on the effectiveness of HBOT for malignant otitis externa did not identify any articles that met the inclusion criteria. The authors did identify a number of case series and case reports, mainly comparing adjunctive HBOT with standard antibiotic treatment. As a result there was no clear evidence to support the use of HBOT for this indication and the authors highlight the need for a well-conducted RCT.

4.19.12 Conditions not meeting inclusion criteria

Two recent HTA reports were brought to the attention of the reviewers by stakeholders. These did not meet the inclusion criteria as they considered treatment in paediatric populations. However, as the reports considered lifelong conditions they are described below.

AETMIS published reports on the use of HBOT for autism and cerebral palsy.

The report on autism identified three case series and two case studies, showing a trend towards positive outcomes for HBOT. However, the authors concluded that there is currently insufficient evidence to support use amongst individuals with autistic disorders. The report identified a number of ongoing studies which may provide further evidence. There are current trials of HBOT for autism (details are presented in Appendix 7) that may provide further evidence of an effect.

The report on cerebral palsy identified five before and after comparator studies and three RCTs. The RCT results conflicted and have been subject to differing interpretation. The report concluded that despite some positive results, there is currently a lack of evidence of effectiveness therefore, HBOT can only be considered experimental and should only be used within the context of clinical trials.
5 SAFETY

The British Hyperbaric Association has produced a code of practice giving guidance on the safe operation of therapeutic hyperbaric facilities. The code of practice covers: the necessity of having standard operating procedures for working practices, including actions to be taken in emergency situations; the requirement for competent adequately-trained staff within the facility; the defined responsibilities of particular staff members; the potential hazards within a hyperbaric facility and the implementation of risk assessments; and the requirement for documented emergency procedures.

The code of practice highlights a number of specific hazards including the risk of patients and attendant staff suffering decompression sickness and barotrauma, and the risks associated with toxicity including convulsions due to cerebral oxygen toxicity. Other hazards associated with hyperbaric facilities are exposure to noise, fire risk, thermal stress and risk of manual handling injuries.

There is a requirement for hyperbaric facilities to carry out risk assessments under the UK Health and Safety regulations. The hazards identified above will be included in these risk assessments and in standard operating procedures, together with contingency measures for foreseeable emergencies.

The code of practice indicates that clinical assessment of the risk and benefits of HBOT for individual patients is the responsibility of the medical director of the facility.

Two HTAs covering a range of indications considered the safety of HBOT.

AETMIS identified middle ear barotrauma as the most common adverse effect, with impaired visual acuity being reported following prolonged treatment series. In addition, pulmonary barotrauma and oxygen toxicity were recognised as adverse events. The authors suggested that studies of HBOT adverse effects are few in number, but provided no indication of their method of identifying the literature.

The MSAC report provided a more comprehensive review of safety issues and listed adverse events related to HBOT treatment as myopia, barotrauma, oxygen toxicity, claustrophobia and decompression illness. The authors indicated that barotrauma affects around 2% of patients and that the myopia commonly associated with higher pressures usually resolves spontaneously. However, evidence was also identified which suggested that repeated exposure to HBOT was associated with a high incidence of irreversible visual impairment.

A number of primary studies documenting adverse events associated with HBOT were identified during preparation of this report. The review articles appraised here have reported the adverse events observed in RCTs and other studies. In general HBOT is considered safe with a low complication rate.

As this report is primarily concerned with the efficacy of HBOT, no attempt was made to systematically collect or pool adverse effect data or quantify the nature and rate of such events. However as the intervention is likely to achieve a low level of benefit for many indications, detailed evaluation of adverse effects could contribute to decision making by informing on the risk:benefit ratio.
6 COST EFFECTIVENESS

6.1 Introduction

This section summarises the available evidence on the cost effectiveness of HBOT as mono- or adjunctive therapy compared with standard treatment.

6.2 Methodology

Evidence for this section of the report was obtained from searching bibliographic databases and websites for literature, scanning the reference lists of retrieved papers for other relevant studies, and also through submissions from interested parties.

6.2.1 Literature searching

The NHS EED, HEED and websites of health economics research units were searched for relevant economic evaluations. A copy of the strategy used to search the MEDLINE database is presented in Appendix 2 and this strategy was adapted to search other databases.

A separate systematic literature search for economic studies was not performed in MEDLINE or EMBASE. Instead clinical effectiveness data were examined for relevant economic information. In addition, a small number of studies were identified by scanning the bibliographies of items retrieved as part of the submission process.

6.2.2 Study selection criteria

The following criteria were applied in the selection of studies for inclusion:

- English language studies only
- conducted in individuals over 16 years of age
- HBOT used either as a mono- or adjunctive therapy for the treatment or management of clinical conditions
- the comparator was the current standard UK treatment or placebo HBOT
- studies which considered both costs and outcomes
- cost-analysis studies were based on UK settings.

All study designs were considered of potential relevance. No date restrictions were applied.

The electronic search yielded 86 references. Full text articles were obtained for 14 of these, and the others were excluded as irrelevant on the basis of the title or abstract. Of the 14 studies, five met the inclusion criteria. A further two studies were identified from the reference lists of studies included in the clinical effectiveness analysis. Selection was carried out independently by two reviewers, and disagreement was resolved by consensus.

The quality of the studies was assessed using the Drummond et al.10-item checklist.

Evidence found

Data were extracted from the studies and are presented in Appendix 5. All data extraction was quality assured by a second reviewer. Excluded studies are listed in Appendix 6.

6.2.3 Types of study and setting

Of the eight studies meeting the inclusion criteria, five were full economic evaluations, and three were cost-analysis papers from the UK. The five economic evaluations comprised two cost-utility analyses and three cost-effectiveness studies. None of the economic evaluations were based on UK settings; two evaluations were Canadian, two were from the USA, and one was undertaken in Australia. Two of these studies were undertaken as part of HTAs.

6.2.4 Indications considered

The majority of the studies were concerned with management of diabetic foot ulcers. The last study also covered non-diabetic wounds, necrotising soft-tissue infections and the prevention of ORN. The prophylactic use of HBOT in patients at risk of ORN was also considered by Dempsey. None of the economic evaluations were based on UK settings; two evaluations were Canadian, two were from the USA, and one was undertaken in Australia.

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Given the variety of indications covered and the different types of study and outcomes measured, it was impossible to consider the findings together. Consequently the four studies relating to diabetic foot ulcers will be discussed, with other studies being considered separately.

6.3 Results

6.3.1 Diabetic foot ulcers

The review undertaken in the clinical effectiveness section of this report identified evidence that HBOT can significantly reduce the need for major amputation for diabetic foot ulcers compared with standard care alone. There was no strong evidence regarding the other outcomes of proportion and area of wounds healed. Efficacy measures used in the economic literature were derived from the same studies as those included in the clinical effectiveness review. The values used for the incidence of amputation were broadly similar to those presented in the clinical effectiveness literature. Wound healing input values were derived by summing the data from individual studies, rather than by combining the results statistically. The measures obtained were, therefore, indicative of the general direction of beneficial effect, but represent an approximation and must be interpreted with caution.

While the patient groups and efficacy and outcomes measures varied in the four diabetic foot ulcer studies, they were consistent in the finding that HBOT appeared broadly cost effective compared with standard care alone or placebo HBOT.

The CADTH study found that the 12-year health service costs of HBOT therapy plus standard care were lower than those for standard care alone. The quality adjusted life years (QALYs) gained by patients receiving HBOT therapy plus...
standard care were also greater than for patients receiving standard care. HBOT plus standard care remained the dominant strategy following sensitivity analysis.

The data for the CADTH report were derived from a previous study undertaken in the USA\textsuperscript{194}. In the USA study, the HBOT arm was not cost saving but the results showed an incremental cost effectiveness ratio (ICER) at 12 years of $2,255 (approximately £1,100) per QALY gained. Scenario analysis showed cost effectiveness to be highly sensitive to the outcome probabilities used, with 12-year ICERs ranging from $-6,011 to $11,801 (approximately -£3,370 to £5,750) per QALY gained.

MSAC\textsuperscript{8} calculated ICERs for amputations avoided in diabetic patients receiving HBOT compared with those receiving usual care. The time horizon for this study was not specified, but it was assumed to be 1 year. The ICER presented was 22,054 Australian dollars (AUD) (approximately £10,000) per amputation avoided.

The Abidia et al.\textsuperscript{198} study did not calculate an ICER for HBOT therapy. It did, however, show a potential cost saving associated with using adjunctive HBOT of £2,960 per patient treated in the NHS in England.

6.3.2 Indications other than diabetic ulcers

6.3.2.1 Wound healing

The clinical effectiveness review indicated some evidence of improved wound healing using HBOT, however this evidence was not strong enough to draw firm conclusions. The efficacy value used in this economic analysis was derived from the one RCT considered in the clinical review.

MSAC\textsuperscript{8} showed an ICER, for a one third reduction in non-diabetic wound area, of 6,941 AUD (approximately £3,000) for HBOT versus placebo HBOT. As the authors pointed out, the clinical significance of this finding and its long-term potential value is unclear.

6.3.2.2 Soft-tissue infection

The clinical effectiveness literature on HBOT for this indication was considered to be inconclusive, with studies reporting conflicting results. MSAC based their economic evaluation upon an effectiveness estimate from a single study, which showed a statistically significant advantage for HBOT in improving survival. On the basis of this, they estimated the ICER per death avoided at trial completion for patients with necrotising soft-tissue infection to be 16,105 AUD (approximately £7,100). Sensitivity analysis using the 95% confidence interval of the effectiveness estimate suggested an upper value of 71,557 AUD. No consideration was given to incremental survival for patients who had not died by the end of the trial.

6.3.2.3 Osteoradionecrosis

A crude UK cost analysis on the use of HBOT to prevent ORN following dental extraction showed the relative costs of treatment pathways to be dependent on the cost of treating patients with severe ORN involving pathological fracture of the mandible. The cost of treating these patients would need to be in the order of £100,000 for prophylactic HBOT costs to break even. This value was particularly sensitive to the incidence of ORN assumed.

MSAC\textsuperscript{8} estimated the ICER per case of ORN avoided at 28,480 AUD (approximately £12,600), based on clinical effectiveness data from the only RCT for this indication. The authors noted that this does not take into account further potential savings associated with the prevention of ORN, such as avoiding mandibular resection.

Dempsey\textsuperscript{195} compared the incremental costs and effects of a modified HBOT protocol to treat 21 patients with ORN of the mandible with those for a hypothetical cohort of 21 patients with similar baseline characteristics receiving conventional treatment. The modified HBOT protocol was the dominant strategy as it was less expensive than conservative therapy and achieved resolution of three cases more than conservative therapy. The relative number of inpatient days for each treatment group had the most impact on these results.

6.3.2.4 Thermal burns

Cianci et al.\textsuperscript{196} examined the use of HBOT in patients with thermal burns, but did not calculate the ICER of providing therapy. The clinical effectiveness section of this review found that evidence is currently lacking regarding this indication and the calculation of an ICER would be of limited value.

6.3.3 Cost of providing HBOT services

Treweek and James\textsuperscript{197} collected data to estimate the start-up, annual and per-treatment costs of adjunctive HBOT for inpatients in a Scottish teaching hospital. For a monochamber unit without an oxygen recirculation facility, they estimated that the cost per treatment would range from £32 to £41. A key assumption is that the unit treats six patients daily, five days a week for up to 47 weeks per year. The capital costs were amortised over 10-years using discount rates of 3% and 7%. With a recirculation facility, these costs would reduce to £30 and £38. Full details of the costs estimated are provided in Appendix 5.

6.4 Discussion

All economic studies were compromised by the sparse quantity and poor quality of the available clinical effectiveness data. As such the findings are not robust but must be viewed as indicative. There is perhaps greater certainty over the direction of benefit in relation to diabetic foot ulcers, as the findings from all four studies were broadly supportive of the cost effectiveness of HBOT compared with standard care.

The CADTH study\textsuperscript{42} found HBOT to be the dominant strategy though Guo et al.\textsuperscript{194} using the same model, did not. The ICER at 12 years in the Guo et al.\textsuperscript{194} study was fairly small. The difference between the studies can be explained partly by the inclusion of slightly different
primary reports. The scenario analysis undertaken by Guo et al.\textsuperscript{194} showed that the ICERs obtained were highly sensitive to the efficacy estimates used. Also the CADTH study\textsuperscript{12} included appropriate wound care costs, whereas Guo et al.\textsuperscript{194} did not. The mortality estimates in both studies were taken from different sources and a number of cost estimates differed, reflecting variation in costs and resource uses between countries.

Sensitivity analyses undertaken by Guo et al.\textsuperscript{194} and MSAC\textsuperscript{8} showed that the results obtained were sensitive to the efficacy measures and utilities used, the number of HBOT treatments per patient, HBOT cost per treatment, the number of HBOT units in use and amputation costs. All these factors need to be taken into account when setting up an HBOT service.

Two cost studies\textsuperscript{10,197} also illustrated the considerable variations in cost per case for an HBOT facility, which depend on factors such as staffing, operating costs, and the capacity at which the facility is operating.

While the use of HBOT was found by Dempsey\textsuperscript{195} to be the dominant over conservative therapy in the treatment of ORN, this was based upon a 100% success rate for HBOT in treating ORN. This efficacy level has not been replicated in other studies and the assumptions made regarding length of stay were not supported by relevant references. These results should be tested in an RCT with an accompanying economic evaluation.\textsuperscript{115} Regarding the prevention of ORN, the incidence value for ORN on which calculations in the MSAC economic evaluation were based reflect the only RCT evidence available. However some authors have questioned this figure\textsuperscript{115}. The cost-analysis study undertaken by Ward et al.\textsuperscript{115}, suggests that, in a UK context, the cost of treating patients who develop severe ORN is likely to be the major driver of prophylactic HBOT use.

The efficacy results obtained for both wound healing and soft-tissue infection are of limited usefulness, given the unclear value of the outcome measures in the former and the conflicting clinical effectiveness evidence in the latter.

As none of these economic evaluations were undertaken in a UK setting, they are of limited applicability to the NHS. The diabetic foot ulcers studies identified suggest that HBOT in addition to standard care is potentially cost effective compared with standard care alone. This would depend on the set up of the facility and the implementation of guidelines ensuring efficient use. Where the NHS commissions hyperbaric services from other providers, such as in Grampian, the costs per treatment and the number of treatments given are important. The Abidia\textsuperscript{198} cost-analysis study provides a fairly recent indication of likely UK costs for treating diabetic foot ulcers using HBOT, as does Ward et al.\textsuperscript{115} for ORN management.

An HBOT facility is unlikely to be used to treat a single indication, and thus its overall cost effectiveness would depend on the case-mix treated. Determining an ICER for the facility as a whole would depend on combining ICERs for each indication, weighted according to the number of patients with each condition. However, the outcomes measured for different treatment indications differ and no economic evaluation has been able to produce an overall cost estimate. In the published literature, Scottish cost data for the setup, running and per treatment costs of an HBOT facility are reported in the Dundee study\textsuperscript{197}. These costs do not generalise to centres that require to keep space available for diving accidents or centres with spare capacity although sufficient data is provided to estimate costs for a service running at less than full capacity. The assumptions used in the report regarding patient throughput and also the treatment protocol have been queried (Dr JA Ross, Senior Lecturer, University of Aberdeen. Personal communication, January 2008). An Evidence Note undertaken by NHS QIS in 2007\textsuperscript{199} reports the charge levied by the Hyperbaric Medicine Unit in Aberdeen per osteoradionecrosis treatment session to be £32\textsuperscript{198}. This figure appears similar to the Dundee costs but it is based upon a different set of circumstances and funding arrangements, and covers consumables only. In contrast to Dundee, this unit is funded by the NHS as a national service required to provide emergency cover for decompression sickness\textsuperscript{199}. A report produced for the National Services Advisory Group of NHSScotland in 2004 to examine the provision of HBOT services in Scotland, provides details of the costs and current funding arrangements for HBOT services (www.nso.scot.nhs.uk/services/hyperbarics/hyperreport.pdf).

To allow better estimation of the cost effectiveness of HBOT therapy, economic evaluation should be incorporated into clinical trials. If not feasible, clinical trials with larger sample sizes and long-term follow up of subjects need to be conducted. Efforts should be made to measure clinically relevant outcomes that enable utilities to be calculated. This would facilitate decision making, by allowing comparisons between indications and with other interventions.
7 DISCUSSION AND CONCLUSIONS

This review of the clinical and cost effectiveness of HBOT has highlighted a number of practical and methodological challenges in conducting a systematic review of a therapy that is used across a very wide range of indications. These include management of the volume of published reports, appropriate application of evidence hierarchies, appropriate methods for synthesising secondary evidence and making robust recommendations when data are sparse or non-existent.

7.1 Identification of studies

The approach taken in this assessment was to use an existing horizon scanning report from AHRQ, which included a search for evidence from 1966–December 2005. Although a limited set of databases were searched this was supplemented by hand searching of text books and reference lists. The AHRQ report included studies of any size and design and reported on indications for which only case studies were available. Rather than duplicating this effort, all publications identified by AHRQ were obtained, and additional literature searches were undertaken for papers published after 2005. This reduced the number of titles and abstracts to be reviewed. Nevertheless some 2,000 publications on HBOT published from 2005–July 2007 were identified, many considering novel indications.

An exception to this protocol was made for searches of the literature on decompression illness. This was not included in the original AHRQ publication, on the basis that HBOT is the standard treatment for this condition. However, in the interest of completeness, searches were conducted for all publications relating to the use of HBOT for decompression illness published from 1966–October 2007.

7.2 Inclusion of studies

Evidence hierarchy was applied to our review of the identified literature. Where an existing HTA or systematic review was available, studies other than more recent RCTs were not considered further. Where both controlled trials and other study designs were identified, case series and case studies were not given further consideration. For many conditions for which HBOT is currently approved by UK or European authorities at least controlled trial evidence was available. What was unexpected was that, although several systematic reviews or HTAs might be published on HBOT use for a particular condition, the original trial evidence was sparse. For example in the case of prevention and treatment of ORN, despite four HTAs and seven systematic reviews being published, these identified only one trial on prevention and one trial on treatment. The primary evidence base was, therefore, extremely small.

The justification for basing this review on controlled trials or higher level evidence can be exemplified by the work on stroke. As McDonagh et al. highlighted, the results of observational studies can show very positive effects in favour of the experimental intervention but, as a result of design flaws, these cannot be attributed to HBOT. The RCTs of stroke patients treated with HBOT failed to show evidence of effectiveness. The principal flaw in case series and case studies tended to be a likelihood of selection bias. Very few reports provided detail on how patients were selected. It is, of course, equally possible that selection bias would work against HBOT, in which case RCT evidence could demonstrate an effect despite none being observed in case studies or non-consecutive case series.

The evidence supporting the use of HBOT for decompression illness is not based on controlled trials, as there is no standard alternative treatment. In addition, the natural history of the condition has shown that non-treatment can result in severe disability or death. For this condition further evidence on the timing of effective treatment schedules or gas mixtures could be obtained by using registry data. The relative effectiveness of different treatment schedules or mixtures of gases could also be tested in controlled trials. Registry data could also be used to clarify effectiveness for conditions such as severe CO poisoning, for which HBOT is considered standard treatment by some health authorities though the existing trials have shown conflicting evidence of efficacy.

7.3 Quality of studies

For most conditions where HTAs or systematic reviews were identified, they were well conducted and the recommendations were generally consistent with the findings. However the primary evidence base for these reviews tended to be of low quality, as RCTs were not well conducted or were inadequately reported. This compromised the robustness of any recommendations. At a practical level, blinding participants to their group allocation can be difficult unless the trial includes sham HBOT. However, other aspects such as the use of appropriate randomisation methods, allocation concealment, and assessor blinding are less difficult but were often not consistently carried out or reported appropriately.

Given the number of conditions for which secondary evidence concerning HBOT is available, reviews were used to provide summary supporting data for many indications. The advantage of such an approach is that primary evidence does not have to be obtained and the data extracted, interpreted and reported. Rather the findings of each review of a particular condition are considered together. The drawback of this approach is that the reviews tend to be based on the same or a similar group of trials. Therefore, eg a set of five systematic reviews, based on three small randomised trials, might appear as a stronger evidence base than exists with studies being ‘double-counted’ in multiple review articles. However, considering the results of a number of reviews together can help to overcome variations in individual reviewer or review group’s interpretations of trial quality and outcomes. This variation was particularly apparent in the quality assessment of studies on traumatic brain injury (Section 4.8) where the Cochrane and AHRQ reports
differed in their assessment of one trial. Similarly, in the section on stroke (Section 4.7) one review indicated that quantitative pooling of outcomes was not possible, whereas another review pooled mortality outcome data from the same group of trials. Despite variations in study inclusion, interpretation and data synthesis, the overall findings of the secondary reports concurred raising confidence in the final conclusions.

There do not appear to be defined methodologies for reviewing reviews but, given the increasing duplication of secondary synthesis, it is likely that this issue will need to be addressed by the evidence-based healthcare community. In the meantime, we took a pragmatic approach and used existing reviews to develop our conclusions. As much of the original synthesis was narrative rather than quantitative this would seem appropriate.

7.4 Overall findings

For the majority of conditions the existing clinical effectiveness evidence did not support routine use of HBOT as a therapeutic intervention. In many instances, there appeared to be trends towards positive outcomes for patients receiving HBOT, but this could not be used as justification for routine application of the technology. Practical issues associated with providing HBOT were not assessed within this report. These considerations are best appreciated when considering using HBOT in the treatment of acute coronary syndrome. Even if the trend towards improved outcomes for acute coronary syndrome patients is reflective of a real therapeutic effect, HBOT is unlikely to be used in the management of these patients as providing HBOT to the substantial acute coronary syndrome patient population would create a considerable organisational challenge.

Care also needs to be taken when interpreting an evidence base as being insufficient to support use of HBOT for a particular condition. The use of hyperbaric oxygen as standard care for decompression illness and CO poisoning is not supported by RCT level data. As has been highlighted by other authors\(^\text{180}\) the evidence base for many standard clinical care practices is similarly limited. Nevertheless for many HBOT indications, RCTs could be readily designed to provide evidence to justify the opportunity cost. This is applicable to conditions where alternative therapies are not available or the natural history of the disease is such that case series cannot provide sufficient high quality data.

HBOT has been used for a large number of conditions for which there are not clear treatments of choice and where clinical opinion on the effectiveness of the currently used interventions differs. For these conditions, assessing the relative effectiveness of all these therapies may provide more useful information for decision making.

Adverse events associated with HBOT have not been systematically reported by many studies. Although there are reports of cases of barotrauma and temporary myopia, HBOT is generally considered safe. However the relative benefits and potential harm are worth consideration, particularly for the many conditions where there is a lack of efficacy evidence\(^\text{192}\).

Although clinical effectiveness evidence was available for many of the conditions originally identified as potentially warranting HBOT, the cost-effectiveness evidence base was much smaller. The majority of publications to date considered the use of HBOT for wounds, in particular diabetic foot ulcers. The only other conditions for which evidence was identified were necrotising soft-tissue infections, ORN and thermal burns. Therefore it is difficult to classify HBOT indications according to whether they are clinically and/or cost effective, as required by the report commissioners and outlined in the study protocol. As a result of the scarcity of supporting evidence the only condition (not considering decompression illness) for which HBOT would appear both clinically and cost effective is in the treatment of diabetic foot ulcers.

7.5 Conclusions

A summary of the findings of this report is presented in Table 7.5-1. It has proved difficult to classify the conditions into one of the four categories:

- of proven lack of effectiveness – not for use.
- of unproven benefit but with sufficient suggestion of possible benefit for trials to be worth doing – use in trials only
- of proven benefit and cost-effective, so should be used in the NHS
- of proven benefit but not cost-effective, so should not be used in the NHS

The only indication for which there was a body of cost-effective evidence was diabetic foot ulcer. For many conditions there may be some evidence of effectiveness but this has been derived from case series or clinical trials that were poorly conducted or reported, and therefore cannot be considered robust. In these cases, a well-designed RCT may help to provide definitive evidence.

For some conditions there was a reasonable body of clinical effectiveness evidence but the findings conflicted. Again, a well-designed large RCT may provide better data. A number of RCTs are currently underway and these are listed in Appendix 7.

For decompression illness and CO poisoning, HBOT use is supported by a good theoretical basis, long-standing use and clinical consensus, despite a lack of RCT evidence. It would be difficult to justify further trials in these treatment areas.
Table 7.5-1  Summary of HBOT findings

<table>
<thead>
<tr>
<th>Condition</th>
<th>European consensus conference recommendations²</th>
<th>Report findings</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompression illness</td>
<td>Major accidents should be treated using hyperoxygenation tables at moderate or high pressure. Minor accidents (pain only) should be treated with recompression tables at a maximum of 2.8 atmospheres absolute (ATA).</td>
<td>Empirical evidence together with the theoretical basis and clinical consensus supports the use of HBOT as standard care.</td>
<td>4.2</td>
</tr>
<tr>
<td>Gas embolism</td>
<td>HBOT strongly recommended.</td>
<td>Empirical evidence is lacking, but the theoretical basis and clinical consensus supports the use of HBOT as standard care in severe cases.</td>
<td>4.2</td>
</tr>
<tr>
<td>Carbon monoxide (CO) poisoning</td>
<td>HBOT is strongly recommended for patients with diagnosed CO poisoning, who are at high risk (unconscious; clinical neurological, cardiac, respiratory or psychological symptoms; pregnant women) of immediate or long-term complications.</td>
<td>Empirical evidence together with theoretical basis and clinical consensus supports the use of HBOT as part of algorithms for the management of CO poisoning.</td>
<td>4.3</td>
</tr>
<tr>
<td>Diabetic lower extremity ulcers</td>
<td>HBOT is recommended if peri-lesional transcutaneous oxygen pressures, measured under hyperbaric conditions, are higher than 100 mmHg.</td>
<td>There is some evidence which indicates that HBOT is effective in reducing the number of major amputations required. Ongoing large clinical trials should provide further evidence which may provide support for the routine use of HBOT (see Appendix 7).</td>
<td>4.4.1</td>
</tr>
<tr>
<td>Non-diabetic wounds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous ulcers</td>
<td>HBOT is recommended if peri-lesional transcutaneous oxygen pressures measured under hyperbaric conditions are higher than 50 mmHg.</td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.4.3.1</td>
</tr>
<tr>
<td>Pressure ulcers</td>
<td></td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.4.3.2</td>
</tr>
<tr>
<td>Other chronic wounds</td>
<td></td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.4.3.3</td>
</tr>
<tr>
<td>Crush injuries</td>
<td>HBOT is strongly recommended in post-traumatic crush injury of Gustilo type III B and C. Measurement of transcutaneous oxygen pressure is recommended to confirm the indication and to direct treatment.</td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.4.3.4</td>
</tr>
<tr>
<td>Blunt chest injury</td>
<td></td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.4.3.5</td>
</tr>
<tr>
<td>Calciphylaxis</td>
<td></td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.4.3.6</td>
</tr>
<tr>
<td>Grafts and flaps</td>
<td>HBOT is recommended for compromised skin grafts and myocutaneous flaps. Measurement of transcutaneous oxygen pressure is recommended to confirm the indication and to direct treatment.</td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.4.3.7</td>
</tr>
<tr>
<td>Condition</td>
<td>European consensus conference recommendations</td>
<td>Report findings</td>
<td>Section</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Necrotising soft-tissue infections</td>
<td>HBOT is strongly recommended for the treatment of anaerobic or mixed bacterial necrotising soft tissue infection.</td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.5.1</td>
</tr>
<tr>
<td>Surgical site infections</td>
<td></td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.5.2</td>
</tr>
<tr>
<td>Livedoid vasculopathy</td>
<td></td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.5.3</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.6</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>The evidence does not support the use of HBOT.</td>
<td>4.7</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td></td>
<td>There is insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.8</td>
</tr>
<tr>
<td>Soft-tissue radionecrosis</td>
<td></td>
<td>There is evidence to support the use of HBOT for patients with radiation-induced proctitis. There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care for patients with other forms of soft-tissue radionecrosis.</td>
<td>4.9</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>HBOT is strongly recommended for radionecrosis of the mandible and recommended for radionecrosis of other bones.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.10</td>
</tr>
<tr>
<td>Cancers and tumour sensitisation to radiotherapy</td>
<td>HBOT is recommended as adjunctive therapy for patients with stage IV neuroblastoma.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care. Ongoing large clinical trials should provide further evidence (see Appendix 7). The adverse events associated with HBOT combined with radiotherapy need to be further evaluated.</td>
<td>4.11</td>
</tr>
<tr>
<td>Orthopaedics</td>
<td>HBOT is recommended for chronic refractory osteomyelitis.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.12</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.13</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.13.1</td>
</tr>
<tr>
<td>Urology</td>
<td></td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.14</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>The evidence does not support the use of HBOT.</td>
<td>4.15</td>
</tr>
<tr>
<td>Condition</td>
<td>European consensus conference recommendations</td>
<td>Report findings</td>
<td>Section</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------------------------</td>
<td>-----------------</td>
<td>--------</td>
</tr>
<tr>
<td>Hearing disorder</td>
<td>HBOT is recommended for sudden deafness but awaits the results of ongoing (2004) RCTs.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.16</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>There is currently insufficient evidence to support the use of HBOT.</td>
<td>4.17</td>
</tr>
<tr>
<td>Thermal burns</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>There is currently insufficient evidence to support the use of HBOT to treat thermal burns.</td>
<td>4.18</td>
</tr>
<tr>
<td>Sports injuries</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.1</td>
</tr>
<tr>
<td>Osteonecrosis of the mandible</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.2.1</td>
</tr>
<tr>
<td>Peridontitis</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.2.2</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.3</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.4</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.5</td>
</tr>
<tr>
<td>Pain syndromes</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.6</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>HBOT is optional when second or third degree burns exceed 20% of the body surface.</td>
<td>The evidence does not support the use of HBOT.</td>
<td>4.19.7</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>HBOT is optional in acute ophthalmological ischaemia.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.8</td>
</tr>
<tr>
<td>Infertility</td>
<td>HBOT is optional in acute ophthalmological ischaemia.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.9</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>HBOT is optional in acute ophthalmological ischaemia.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.10</td>
</tr>
<tr>
<td>Malignant otitis externa</td>
<td>HBOT is optional in acute ophthalmological ischaemia.</td>
<td>There is currently insufficient evidence to support the routine use of HBOT as an adjunct to standard care.</td>
<td>4.19.11</td>
</tr>
</tbody>
</table>
8 Acknowledgements

8  ACKNOWLEDGEMENTS

NHS Quality Improvement Scotland is grateful to those who have provided input into this report including the commissioners, peer reviewers and stakeholders who commented on earlier drafts (see Appendix 1).

We hope this report has achieved the important goal of sharing knowledge and best practice across Scotland.
9 REFERENCES

NB: In some cases papers included in synthesised reports are identified within tables in this report but citations are not included below.


2. European committee for hyperbaric medicine. 7th European consensus conference on hyperbaric medicine. 2004 December 3-4; Lille, France. 2004.


42. Canadian Agency for Drugs and Technologies in Health. Adjunctive hyperbaric oxygen therapy for diabetic foot ulcer: an economic analysis. 2007 [cited 2008 Apr 14]; Available from: http://www.cadth.ca/media/pdf/274_HBOT_tr_e.pdf


References


APPENDICES
10 APPENDICES

Appendix 1  NHS QIS Project Team, Report Commissioners, Peer Reviewers and other contributors

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Other contributors

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Mr Philip Sayers  Managing Director  London Hyperbaric and Wound Healing Centre
Appendix 2  Strategy for literature searches

Clinical effectiveness: secondary literature

A search to identify HTAs, systematic reviews and other evidence-based reports was undertaken in July 2007 using the following resources:

- Agency for Health Care Research and Quality (AHRQ) www.ahrq.gov
- Alberta Heritage Foundation for Medical Research www.ahfmr.ab.ca/
- Agence d’Évaluation des Technologies et de Modes d’intervention en Santé (AETMIS) www.aetmis.gouv.qc.ca/site/home.phtml
- Canadian Agency for Drugs and Technologies in Health www.cadth.ca/
- Canadian Medical Association http://mdm.ca/cpgsnew/cpgs/index.asp
- Centre for Clinical Effectiveness (Australia) www.monash.edu.au/
- Centers for Medicare and Medicaid Services www.cms.hhs.gov/
- Centre for Reviews and Dissemination (CRD), University of York www.york.ac.uk/inst/crd/index.htm
- CIGNA www.cigna.com/index.html
- Chief Scientists Office (CSO) www.sehd.scot.nhs.uk/cso/
- Clinical Evidence www.clinicalevidence.com/cweb/index.jsp
- Cochrane Database of Systematic Reviews via the Cochrane Library (Internet)
- Database of Abstracts of Reviews of Effects (DARE) via the Cochrane Library (Internet) and Centre for Reviews and Dissemination (CRD)
- ECRI www.ecri.org/Pages/default.aspx
- Health Services Research Unit (HSRU) www.abdn.ac.uk/hsru/
- Health Technology Assessment database via the Cochrane Library (Internet)
- International Clinical Trials Registry www.who.int/ictrp/search/en/index.html
- National Collaborating Centre for Health Technology Assessment (NCCHTA) www.ncchta.org/
- Medical Service Advisory Committee – Australia www.mmsc.gov.au/
- National Institute for Clinical Excellence (NICE) www.nice.org.uk/
- National Electronic Library for Health www.york.ac.uk/inst/crd/index.htm
- National Health and Medical Research Council (NHMRC) www.nhmrc.gov.au/publications/index.htm
- New Zealand Guidelines Group www.nzgg.org.nz/
- Scottish Health on the Web (SHOW) www.sehd.scot.nhs.uk/
- Scottish Intercollegiate Guidelines Network (SIGN) www.sign.ac.uk/
- Swedish Council on Technology Assessment in Health Care (SBU) www.sbu.se/www/index.asp
- Translating Research into Practice (TRiP) www.tripdatabase.com/index.html
- UpToDate www.uptodate.com/
- US National Institutes of Health www.nih.gov/

Clinical effectiveness: primary literature

The following resources were searched in July 2007 for primary literature:

- MEDLINE (OVID)
- MEDLINE In-Process (OVID)
- EMBASE (OVID)
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library
- Web of Science (ISI)
- Current Controlled trials www.controlled-trials.com/
- Trials Central www.trialscentral.org/
- National Research Register www.nrr.nhs.uk/

Search 1: Hyperbaric oxygen therapy

1. Hyperbaric Oxygenation/
2. hyperbar$.tw.
3. (chamber$ adj2 (oxygen$ or monoplace or multiplace or "atmosphere exposure").tw).
4. (HBO or HBOT or HDO or HDOT).tw.
5. or/1-4
6. limit 5 to yr="2006 - 2007"
7. limit 6 to english language

Search 2: Hyperbaric oxygen therapy for decompression sickness

1. Hyperbaric Oxygenation/
2. hyperbar$.tw.
3. (chamber$ adj2 (oxygen$ or monoplace or multiplace or "atmosphere exposure").tw).
4. (HBO or HBOT or HDO or HDOT).tw.
5. or/1-4
6. Barotrauma/
7. Decompression Sickness/
8. Embolism, Air/
9. barotrauma.tw.
10. (((decompression or caisson or "compressed air" or pressure) adj1 (sickness or disease or illness or trauma)).tw.
11. (((diver or divers or diving) adj2 (disease or palsy or paralysis or bends)).tw.
12. ("arterial air embolism" or "arterial gas embolism" or aeroembolism).tw.
13. "the bends".tw.
14. DCl.tw.
15. or/6-14
16. S and 15
17. limit 16 to yr="1966 - 2005"
18. limit 17 to english language

Economic evaluation: secondary literature

The following sources were searched in July 2007:

- NHS Economics Evaluation Database (NHSEED) via the Cochrane Library (Internet) and Centre for Reviews and Dissemination (CRD)
• Health Economics Evaluation database (HEED) (Internet, subscription)
• Health Economics Research Unit (HERU), University of Aberdeen www.abdn.ac.uk/heru/
• Centre for Health Economics (CHE), University of York www.york.ac.uk/inst/che/
• Centre for Health Economics Research and Evaluation (CHERE), University of Technology, Sydney www.chere.uts.edu.au/
• Health Economics Research Group (HERG), Brunel www.brunel.ac.uk/about/acad/herg/
• University of Southampton www.southampton.ac.uk/socsci/economics/?fromcc
Appendix 3  Review of the evidence retrieved from literature search for hyperbaric oxygen therapy

**Appendix 4  Evidence on using HBOT to treat decompression sickness - case series**

<p>| Study                          | Type       | Aim                                                                 | Search strategy/ characteristics                                                                 | Inclusion/exclusion criteria                                                                                           | Results                                                                                             | Conclusions and comments                                                                 |
|-------------------------------|------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Barratt &amp; Van Meter, 2004&lt;sup&gt;48&lt;/sup&gt;  | Case series | Review of medical records of patient admitted to 2 hyperbaric units in Honduras and Nicaragua. | Review of medical records of (Moskito Indian lobster) divers. Treatment using USA Navy tables 5 or 6, depending on severity of illness and availability of oxygen and/or systemic steroids. | Patients admitted for treatment of decompression sickness or arterial gas embolism 1985–mid 1996. Outpatients were not included. | 229 patients were included, but outcome data were only available for 182. Median delay to presentation was 48h (range 4h–44 days). Overall, 63% of divers received HBOT and 61% systemic steroids. Full recovery was observed in 30% of patients for whom outcome data were available. Most patients experienced symptom improvement. | HBOT had therapeutic efficacy despite long delays before treatment. Missing data prevented comparison of the effectiveness of HBOT and systemic steroids. |
| Elrefaei, 2000&lt;sup&gt;30&lt;/sup&gt; | Case series | Review of cases diagnosed and treated for decompression sickness. | USA Navy table 6 primarily used for therapeutic intervention. | All patients of the Hyperbaric Department of the Princess Haya Hussein Hospital, Aqaba, Jordan from Jan 1994–Dec 1997. | 23 patients were included. It was not clear how many had type I and II decompression sickness. 17 patients required one intervention. Those with residual symptoms were not available for follow up. | Numerical discrepancies compromised interpretation. |
| Ball, 1993&lt;sup&gt;25&lt;/sup&gt;  | Case series | To determine if symptom improvement could be predicted based on initial severity and if the benefit from re-treatment could be predicted based on residual symptom severity. | Records of chamber use from Jan 1998–July 1990 at the Naval Station Subic Bay Ship. Models were developed to assess the relationship between symptom severity and HBOT therapeutic effect. | Cases of spinal cord decompression sickness defined by limb sensory or motor loss that progressed from distal to proximal or included patchy sensation disturbances or paresthesia. | 49 cases were included in the review. USA Navy treatment guidelines were used. 33 cases required re-treatment. A statistically significant relationship was observed between initial and residual symptom severity after all treatments. A relationship was also observed between the time to HBOT and symptom severity after all treatments. | Most divers with mild to moderate symptoms recovered completely, irrespective of time to recompression. Recovery among more severely affected divers was dependent on time to treatment. Response to first treatment did not predict the effectiveness of further treatments for residual symptoms. The authors noted a large proportion (49%) of missing records and the potential for bias. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>Search strategy/ characteristics</th>
<th>Inclusion/exclusion criteria</th>
<th>Results</th>
<th>Conclusions and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aharon-Peretz et al., 1993²⁷</td>
<td>Case series</td>
<td>Review of cases.</td>
<td>Review of dive history, risk factors and outcome. USA Navy table 6 was used for most patients. The 6 most recent cases used heliox 50/50 according to the Comex Treatment Table. Treatment was supplemented by HBOT 2.8 ATA for 90 min twice daily until no further improvement was observed.</td>
<td>Patients with spinal cord symptoms treated at 2 hyperbaric centres in Israel from 1975–1990.</td>
<td>68 patients were included in the study. The average delay from symptoms to recompression was 11 h (0.5–30 h). 78% of patients achieved full recovery. The remaining patients had residual symptoms.</td>
<td>Initial symptoms fail to reflect disease severity and vigorous treatment of all patients is warranted. The authors suggested that alternative decompression schedules using oxygen/helium mixtures should be tested in RCTs.</td>
</tr>
<tr>
<td>Lee et al., 1989²⁰¹</td>
<td>Case series</td>
<td>To review experience of clinical HBOT from 1976–1987.</td>
<td>1,288 patients with a range of conditions (556 with decompression sickness) who were treated with HBOT. Treatment for decompression sickness was according to USA Navy treatment tables, followed by 50 ft for 120 mins when residual symptoms remained after first treatment. Treatment table 6 was subsequently modified to reduce the need for re-treatment.</td>
<td>Exclusions: patients with a range of contraindicated comorbidities, including untreated pneumothorax.</td>
<td>550 patients with decompression sickness were treated 2,877 times (mean number of treatments of 5.2±9.8). Patients were treated from 1–120 times. 420 patients experienced cure, 130 symptom improvement and 6 died. 128 serious cases were retrospectively reviewed to compare the use of US Navy table 6 with the modified table. A statistically significant improvement in cure rate and a reduction in recurrence was seen when the modified table was used.</td>
<td>The USA Navy treatment tables were effective in treating patients with decompression sickness and modification of table 6 improved efficacy.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/ characteristics</td>
<td>Inclusion/exclusion criteria</td>
<td>Results</td>
<td>Conclusions and comments</td>
</tr>
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<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wirjosemito et al., 1989</td>
<td>Case series</td>
<td>To review cases of altitude-related type II decompression sickness, to improve understanding of symptom patterns.</td>
<td>Review of files from the early 1960s–1986. 133 type II cases included some reported by Davis et al., 1977. Cases were classified into 4 severity levels. Treatment was based on USA Navy table 6 with modifications for multiple and extended treatments.</td>
<td>All type II decompression sickness cases treated at USA airforce hyperbaric facilities and all USAF staff treated at other military and civilian chambers.</td>
<td>130 cases (97.7%) achieved full recovery following HBOT, with 3 patients having residual symptoms. There were no deaths.</td>
<td>Conclusions related to the ability to diagnose type II decompression sickness and classify severity, to avoid unnecessary disqualification from service. There was no indication of time to treatment but it was likely to be short, in common with other studies on military personnel.</td>
</tr>
<tr>
<td>Pelosi et al., 1981</td>
<td>Case series</td>
<td>To report on clinical experience of treating decompression sickness.</td>
<td>Clinical review of 64 patients, with all likely to be recreational divers. All patients were admitted to the critical care unit within 4h. Hyperbaric treatment was according to the USA Navy treatment tables.</td>
<td>No indication was given of how patients were selected.</td>
<td>Patients were classified into 3 groups based on illness severity: 16 had mild, 30 moderate and 18 severe symptoms. All patients with mild symptoms recovered. 21 patients with moderate symptoms recovered and there was improvement in the other 9. 1 patient in the severe symptom group recovered, 8 improved and there was no change in the remaining 9.</td>
<td>There was no correlation between depth, time of immersion and symptoms. The authors noted no correlation between treatment delay, clinical outcome and the recompression depth needed to relieve symptoms. They did note a relationship between initial damage and outcome (no statistical analysis). The potential for bias with case series applies.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/ characteristics</td>
<td>Inclusion/exclusion criteria</td>
<td>Results</td>
<td>Conclusions and comments</td>
</tr>
<tr>
<td>-------</td>
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<td>-----------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bayne, 1978</td>
<td>Case series</td>
<td>Retrospective analysis to define success in treating acute decompression sickness at the Naval School, Diving and Salvage, Washington, USA.</td>
<td>Review of narrative summaries of 50 consecutive cases. Treatment using USA Navy tables.</td>
<td>50 consecutive cases over a 3-year period involving military divers (dates not given).</td>
<td>46 of 50 divers were decompressed within 2h of symptom onset. One diver did not experience immediate symptom relief and had residual arm pain for 5 days post-treatment.</td>
<td>The authors attributed the success of therapy to the short time interval from symptom onset to recompression.</td>
</tr>
<tr>
<td>Davis et al., 1977</td>
<td>Case series</td>
<td>To review the use of HBOT to treat altitude decompression sickness.</td>
<td>Review of 145 cases of altitude decompression sickness treated in hyperbaric chambers.</td>
<td>Patients treated in 7 hyperbaric chambers prior to Jan 1977.</td>
<td>Of the 136 cases treated using the USA Navy treatment tables, 135 were symptom free and 1 patient experienced a minor residual defect.</td>
<td>The pattern of symptoms in altitude decompression cases differs from that observed among divers, with more neurological symptoms and fewer cases of spinal cord decompression. The authors concluded that HBOT is highly effective for the treatment of altitude-induced decompression sickness.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>Search strategy/ characteristics</td>
<td>Inclusion/exclusion criteria</td>
<td>Results</td>
<td>Conclusions and comments</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>-------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Erde &amp; Edmonds, 1975</td>
<td>Case series</td>
<td>To review the clinical manifestations of decompression sickness among sport and civilian divers.</td>
<td>100 divers with decompression sickness or who developed symptoms during or after ascent, whose symptoms were relieved by recompression therapy. Study dates were not given and it was unclear if these cases were consecutive or otherwise selected. HBOT therapy was in accordance with USA Navy treatment tables.</td>
<td>Patients with evidence of pulmonary barotrauma were excluded.</td>
<td>Approximately half of patients experienced type I decompression sickness (less severe symptoms such as joint pain) and half more severe type II symptoms. There was no relationship between disease severity and the number of patients deteriorating or showing no improvement (no statistical analysis). There was no indication that delays in therapy of 24h or more reduced treatment efficacy.</td>
<td>Differences in decompression sickness are seen when comparing sport/civilian and Navy divers. The authors commented on the efficacy of HBOT therapy despite considerable delays from dive to treatment. The potential for bias with case series applies.</td>
</tr>
</tbody>
</table>
Appendix 5  
Evidence on the cost effectiveness of HBOT - included and excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treweek &amp; James, 2006(^{197})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>Cost analysis</td>
</tr>
<tr>
<td>Purpose</td>
<td>To estimate the start-up, annual and per-treatment costs of adjunctive HBOT for inpatients.</td>
</tr>
<tr>
<td>Study site and population</td>
<td>Ninewells Hospital, Dundee. Inpatients.</td>
</tr>
<tr>
<td>Intervention</td>
<td>One-chamber hyperbaric unit</td>
</tr>
<tr>
<td>Comparator</td>
<td>None</td>
</tr>
<tr>
<td>Clinical data sources</td>
<td>N/A</td>
</tr>
<tr>
<td>Economic data sources</td>
<td>Primary data gathering</td>
</tr>
<tr>
<td></td>
<td>Cost of inpatient stay not included because the patient would be in hospital regardless of HBOT therapy.</td>
</tr>
<tr>
<td></td>
<td>All costs are for 2004.</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>N/A</td>
</tr>
<tr>
<td>Time horizon</td>
<td>-</td>
</tr>
<tr>
<td>Perspective</td>
<td>NHS</td>
</tr>
<tr>
<td>Discounting</td>
<td>Capital costs amortised over 10 years, calculated using discount rates of 3% and 7%.</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Lower and upper ranges calculated for most inputs.</td>
</tr>
<tr>
<td>Assumptions</td>
<td>Assumed that the chamber is in one of the six large Scottish teaching hospitals.</td>
</tr>
<tr>
<td>Results</td>
<td>Lower and upper range costs for a one chamber HBOT unit (without recirculation):</td>
</tr>
<tr>
<td></td>
<td>Lower (£)</td>
</tr>
<tr>
<td>Capital cost</td>
<td>64,800</td>
</tr>
<tr>
<td>Staff nurse</td>
<td>21,978</td>
</tr>
<tr>
<td>Staff consultant</td>
<td>4,880</td>
</tr>
<tr>
<td>Oxygen</td>
<td>6,812</td>
</tr>
<tr>
<td>Property and cleaning</td>
<td>306</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>132</td>
</tr>
<tr>
<td>General overheads</td>
<td>256</td>
</tr>
<tr>
<td>No. of treatments per year</td>
<td>600</td>
</tr>
<tr>
<td>Cost per treatment</td>
<td>32</td>
</tr>
</tbody>
</table>

(\(\text{including amortised capital costs}\)
### Study

**Study**

Abidia et al., 2003

**Study type**

RCT with costing data

**Purpose**

To examine the role of HBOT in the treatment of diabetic lower extremity ulcers in patients with peripheral arterial disease.

**Study site and population**

18 diabetic outpatients presenting to Hull Royal Infirmary with ischaemic lower extremity ulcers >1 cm but <10 cm diameter not showing signs of healing despite medical management for >6 weeks since presenting.

**Intervention**

Adjunctive HBOT treatment in multi-place chamber for 90 mins daily, 5 days per week, totaling 30 sessions.

**Comparator**

Placebo HBOT for same number of sessions.

**Clinical data sources**

Trial data

**Economic data sources**

NHS reference costs

**Outcome measures**

Ulcer surface area measurement 6 weeks after the end of the intervention; ulcer depth; clinical signs of infection; quality of life assessed by SF36 and HAD scales.

**Time horizon**

1 year

**Perspective**

NHS

**Discounting**

N/A

**Uncertainty**

N/A

**Assumptions**

N/A

**Results**

Charge by Hull Hyperbaric Unit for HBOT therapy=£100 per patient session.
Number of session per patient=30
Total cost £3,000

Cost of an outpatient hospital visit for ulcer dressing=£58
Mean number of visits for dressing ulcer during follow-up year:
  *HBOT group*=33.75 (±62)
  *Control group*=136.5 (±126)
Mean total cost per patient per year for ulcer dressing:
  *HBOT group*=£1,972
  *Control group*=£7,946

Potential cost saving using adjunctive HBOT=£2,960 per patient treated.

**Comments**

Costs will vary among HBOT units.
<table>
<thead>
<tr>
<th>Study</th>
<th>Guo et al., 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>Cost utility analysis using a decision-tree model.</td>
</tr>
<tr>
<td>Purpose</td>
<td>To estimate the cost effectiveness of adjunctive HBOT therapy in the treatment of diabetic foot ulcers.</td>
</tr>
<tr>
<td>Study site and population</td>
<td>Hypothetical cohort of 1,000 patients with severe diabetic foot ulcers all aged 60.</td>
</tr>
<tr>
<td>Intervention</td>
<td>HBOT as adjunct to standard wound care.</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard wound care.</td>
</tr>
<tr>
<td>Economic data sources</td>
<td>Costs were obtained from a costing manual and a published study from 1995. All costs were inflated to 2001 dollars. Utility values – published Swedish study using EQ-5D.</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>QALYs</td>
</tr>
<tr>
<td>Time horizon</td>
<td>1, 5 and 12 years</td>
</tr>
<tr>
<td>Perspective</td>
<td>Societal and payers’ perspective</td>
</tr>
<tr>
<td>Discounting</td>
<td>QALYs discounted at 3%</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Scenario analysis using the least and most efficacious outcomes. One-way sensitivity analysis to assess the impact of each parameter for the base-case estimation over different time periods.</td>
</tr>
<tr>
<td>Assumptions</td>
<td>Mortality rate assumed to be constant over 12-year period. Foot ulcers would not reoccur once they were healed.</td>
</tr>
<tr>
<td>Results</td>
<td>Number of major Lower Extremity Amputations (LEAs) HBOT group=50 Control group=205 Number of minor LEAs HBOT group=175 Control group=130 QALYs gained due to use of HBOT in hypothetical cohort 1 year=50.2 5 years=265.3 12 years=608.7 Number of HBOT treatments per case=29 Cost of HBOT treatment (not specified whether mono- or multi-place)=$407 per treatment session Cost of major LEA per case=$39,404 Cost of minor LEA per case=$40,673 ICERs 1 year=$27,310 5 years=$5,166 12 years=$2,255 After scenario analysis ICER 1 year Worst $142,923 Best -$72,799 Sensitivity analysis The cost-effectiveness ratios were most sensitive to the quality weights, especially for major LEA. The number of HBOT treatments per case, the HBOT cost per treatment, and the treatment costs of major and minor LEA per case also had a significant impact on cost-effectiveness ratios.</td>
</tr>
<tr>
<td>Comments</td>
<td>Efficacy estimates from fairly weak clinical evidence.</td>
</tr>
<tr>
<td>Study</td>
<td>Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé, 2001</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Study type</td>
<td>Cost-benefit analysis conducted as part of HTA.</td>
</tr>
<tr>
<td>Purpose</td>
<td>To inform decision making on whether the wider diffusion of HBOT within Quebec should be supported.</td>
</tr>
</tbody>
</table>
| Study site and population | Quebec, Canada  
Scenario 1 – status quo based on current output of the Hopital du Sacre-Coeur de Montreal’s hyperbaric medical centre.  
Scenario 2 – full capacity, assuming that the facility operates at full capacity. |
| Intervention | HBOT |
| Comparator | N/A |
| Clinical data sources | N/A |
| Economic data sources | Hospitalisation costs calculated from number of cases and mean length of stay data held in administrative database.  
Cost of HBOT based upon operating costs of the Hopital du Sacre-Coeur de Montreal. |
| Outcome measures | Reduction in hospitalisation costs |
| Time horizon | 1 year |
| Perspective | Hospital system |
| Discounting | N/A |
| Uncertainty | Two scenarios considered |
| Assumptions | Assumes that all patients have access to a hyperbaric chamber within an hour’s drive of their home. |
| Results | Hospitalisation costs per year for seven conditions for which HBOT is indicated=36,253,395 CAD (based on daily cost per person of 450 CAD).  
Scenario 1 status quo  
Cost per HBOT treatment session (multiplace)=333 CAD  
Annual operating costs for treating seven conditions for which HBOT indicated=20.4 million CAD.  
To obtain a favourable cost-benefit ratio, HBOT treatments would have to result in a reduction of at least 58% in the mean length of hospital stay.  
Scenario 2 full capacity  
Cost per HBOT treatment session (multiplace)=156 CAD  
Annual operating costs for treating seven conditions for which HBOT indicated=9.6 million CAD.  
To obtain a favourable cost-benefit ratio, HBOT treatments would have to result in a reduction of at least 28% in the mean length of hospital stay. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Medical Services Advisory Committee, 2001*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>Cost-effectiveness analysis as part of HTA</td>
</tr>
<tr>
<td>Purpose</td>
<td>To evaluate the safety, effectiveness and cost effectiveness of HBOT for a number of indications to inform funding decision under the Medicare Benefits Scheme.</td>
</tr>
<tr>
<td>Study site and population</td>
<td>Australia, Medicare Benefits Scheme</td>
</tr>
<tr>
<td>Intervention</td>
<td>Monoplace HBOT</td>
</tr>
</tbody>
</table>
| Comparator | Varied amongst indications:  
  a) Diabetic wounds - standard surgical, infection and diabetic control measures  
  b) Non-diabetic wounds - sham HBOT treatment  
  c) Necrotising soft-tissue infections - standard care  
  d) Osteoradionecrosis - antibiotic regimen |
| Clinical data sources | Efficacy estimates taken from systematic reviews of primary studies conducted in earlier part of the report. Only indications for which clinical effectiveness was observed were included in the cost-effectiveness analysis. |
| Economic data sources | Costs of HBOT were based on expert opinion. Cost offsets estimated from published cost data and inferences from trial data. |
| Outcome measures | Varied amongst indications  
  a) Diabetic wounds - major or minor amputation avoided  
  b) Non diabetic wounds - mean changes in wound area  
  c) Necrotising soft-tissue infections - survival  
  d) Osteoradionecrosis - diagnosis of osteoradionecrosis |
| Time horizon | Not specified |
| Perspective | Healthcare insurance provider |
| Discounting | Not specified |
| Uncertainty | Sensitivity analyses undertaken on the following:  
  Risk difference  
  Number of HBOT sessions  
  Staff costs  
  Number of HBOT units. |
| Assumptions | N/A |
| Results | The different indications for which HBOT is used do not have homogeneous outcomes, therefore it was not possible to calculate a single cost-effectiveness ratio.  
  Average cost of HBOT per course of treatment=6,941 AUD based upon 30 treatment sessions.  
  **Diabetic wounds**  
  Risk reduction in the number of amputations following HBOT=11%  
  Net costs for HBOT treatment minus amputations avoided=242,591 AUD.  
  ICER per amputation avoided=22,054 AUD  
  **Non-diabetic wounds**  
  Difference in reduction in wound area at 6 weeks following HBOT=33%  
  ICER per one third reduction in wound area=6,941 AUD  
  **Necrotising soft-tissue infection**  
  Difference in survival for HBOT group=43.1%  
  ICER per death avoided at trial completion=16,105 AUD  
  **Osteoradionecrosis**  
  24.32% reduction in number of cases of osteoradionecrosis following HBOT  
  Net costs for HBOT treatment - cost of antibiotic regimen=692,748 AUD  
  ICER per case of osteoradionecrosis avoided=28,480 AUD  
  Results after sensitivity analysis |
| Results (continued) | Diabetic foot ulcers  
ICER ranges from comparator treatment dominant to HBOT being cost saving.  
Non-diabetic wounds  
No sensitivity analysis undertaken.  
Necrotising soft tissue infections  
ICER per death avoided at trial completion ranges from 5,368 to 71,557 AUD.  
Osteoradionecrosis  
ICER per case of osteoradionecrosis avoided ranges from 10,081 to 66,187 AUD. |
<p>| Comments | There is considerable uncertainty surrounding the estimates of efficacy. |</p>
<table>
<thead>
<tr>
<th><strong>Study</strong></th>
<th><strong>Cianci et al., 1990</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type</strong></td>
<td>Non-randomised trial with cost-effectiveness analysis included.</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>To measure the impact of using HBOT in addition to standard care for patients with 19–50% total body surface area burns, on reducing length of hospital care and cost of care.</td>
</tr>
<tr>
<td><strong>Study site and population</strong></td>
<td>21 patients aged 14–47 years with total body surface burns of 19–50% who were inpatients at a burns centre in California.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>HBOT administered in a monoplace chamber as an adjunct to standard care.</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Standard care (details not stated)</td>
</tr>
<tr>
<td><strong>Clinical data sources</strong></td>
<td>Non-randomised trial</td>
</tr>
<tr>
<td><strong>Economic data sources</strong></td>
<td>Costs and resource use not reported separately. Total costs for trial groups collected retrospectively from hospital records. Costs based on 1987 USA dollars.</td>
</tr>
<tr>
<td><strong>Outcome measures</strong></td>
<td>Number of surgical procedures for debridement and grafting. Hospital length of stay.</td>
</tr>
<tr>
<td><strong>Time horizon</strong></td>
<td>Period of study only</td>
</tr>
<tr>
<td><strong>Perspective</strong></td>
<td>Health service provider</td>
</tr>
<tr>
<td><strong>Discounting</strong></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Uncertainty</strong></td>
<td>No allowance made</td>
</tr>
<tr>
<td><strong>Assumptions</strong></td>
<td>None stated</td>
</tr>
</tbody>
</table>
| **Results** | Mean length of stay
HBOT plus standard care=43.2 days (range 20–81 days)
Standard care alone=28.4 days (range 13–60 days)

Mean number of surgical procedures
HBOT plus standard care=1.7 (range 0–4)
Standard care alone=2.8 (range 0–8)

Mean cost of hospital care
HBOT plus standard care=$60,350 (range $27,000–$131,000)
Standard care alone=$91,960 (range $24,700–$210,000)

Synthesised cost and outcome results were not presented. |
<p>| <strong>Comments</strong> | The shorter length of stay for HBOT group was statistically significant but no power calculation was mentioned and the clinical significance was not discussed. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Dempsey, 1997&lt;sup&gt;95&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>Cost-effectiveness analysis</td>
</tr>
<tr>
<td>Purpose</td>
<td>To compare the incremental costs and effects of a modified HBOT protocol with the conservative treatment of ORN of the mandible.</td>
</tr>
<tr>
<td>Study site and population</td>
<td>21 patients who underwent a modified HBOT protocol at the Hamilton Civic Hospitals, Hamilton, Ontario.</td>
</tr>
<tr>
<td>Intervention</td>
<td>The Marx HBOT protocol was modified so that the treating physician could use their discretion to determine the number of dives that a patient would undergo at each stage of the protocol according to healing.</td>
</tr>
<tr>
<td>Comparator</td>
<td>Hypothetical group of 21 patients with same demographics undergoing conservative treatment.</td>
</tr>
<tr>
<td>Clinical data sources</td>
<td>For the study group - outcomes achieved. For the hypothetical group - outcomes from five studies published from 1971–1992.</td>
</tr>
<tr>
<td>Economic data sources</td>
<td>For study group costs measured directly. For comparator group costs calculated based upon hypothetical outcomes.</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>Wound healing</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Not specified (time to complete the Marx protocol)</td>
</tr>
<tr>
<td>Perspective</td>
<td>Societal</td>
</tr>
<tr>
<td>Discounting</td>
<td>5%</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Sensitivity analysis undertaken using the range of values reported in the literature for healing following conservative treatment. Cost per inpatient day, average number of inpatient days, cost of reconstructive surgery and nature of the HBOT protocol followed were also varied.</td>
</tr>
<tr>
<td>Assumptions</td>
<td>It was assumed that all HBOT patients consumed that same amount of supplies, and that all inpatients consumed the same amount of resources. The average per patient cost of one round of the modified HBOT protocol was added to the costs of the 3 patients who would not have healed under conservative therapy, assuming that one round of the HBOT protocol would lead to resolution of their disease.</td>
</tr>
<tr>
<td>Results</td>
<td><strong>Effectiveness</strong>&lt;br&gt;Modified HBOT protocol group&lt;br&gt;57% patients healed during stage I&lt;br&gt;34% patients healed during stage II&lt;br&gt;9% patients healed during stage III&lt;br&gt;&lt;br&gt;<strong>Conservative treatment group</strong>&lt;br&gt;65% patients would heal before reconstructive surgery&lt;br&gt;23% patients would heal after reconstructive surgery&lt;br&gt;12% would not have experienced disease resolution&lt;br&gt;&lt;br&gt;<strong>Costs</strong>&lt;br&gt;Total cost to treat 21 HBOT protocol patients 10,064 CAD&lt;br&gt;Total cost to treat 21 hypothetical patients 1,327,444 CAD&lt;br&gt;&lt;br&gt;Total cost of the modified HBOT protocol was less expensive and 3 more cases resolved than with conservative therapy, therefore the modified HBOT protocol was considered the dominant strategy. Sensitivity analysis showed the most significant factor affecting the results to be the number of inpatient days.</td>
</tr>
<tr>
<td>Comments</td>
<td>The authors noted that an RCT was not appropriate as it would contravene the current standard of practice.</td>
</tr>
<tr>
<td>Study</td>
<td>Ward et al., 2000</td>
</tr>
<tr>
<td>-------</td>
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</tr>
</tbody>
</table>

### Study type
Cost analysis

### Purpose
Modelling was undertaken to provide a crude indication of the cost effectiveness of HBOT in the prevention of ORN following dental extraction.

### Study site and population
Hypothetical English health authority serving 500,000 population, with 5 patients who had undergone radiotherapy treatment requiring dental extractions.

### Intervention
Prophylactic HBOT prior to dental extractions

### Comparator
Absence of prophylactic HBOT

### Clinical data sources
Not specified

### Economic data sources
HBOT costs from Plymouth Diving Disease Research Centre. Hospital costs – not specified.

### Outcome measures
Prevention of ORN

### Time horizon
Not specified

### Perspective
Not specified. Assumed to be NHS.

### Discounting
None

### Uncertainty
Sensitivity analysis undertaken on the incidence of ORN, probability of patients progressing to worst-case scenario and the effectiveness of HBOT.

### Assumptions
- The incidence of ORN following extraction is 5.8%.
- Effectiveness of HBOT in the prevention of ORN is 80%.
- Patients who develop ORN are either treated successfully by a single course of HBOT, or progress to the ‘worst-case scenario’ with a pathological fracture of the mandible.
- For patients developing ORN, the probability of advancing to the worst-case scenario is 55%.
- Worst-case scenario patients will require HBOT treatment and surgery, medication and additional hospital care.

### Results
The relative costs of HBOT and non-HBOT options are dependent on the cost of treating the worst-case scenario. At a cost of £20,000, the expected cost per annum of the HBOT pathway is four times the expected cost of the non-HBOT pathway. The cost of treating the worst-case scenario would need to be £100,000 for the cost of both options to break even.

Sensitivity analysis found the break-even cost to vary from £17,500–£127,500.

### Comments
The figures presented were only intended by the authors to give a broad estimate of the costs of using HBOT for this indication, and were not intended to be precise.

The authors acknowledged the importance of quality of life for these patients and noted that this is not considered in the crude analysis undertaken.
### Appendix 6  Cost effectiveness - excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>John-Baptiste <em>et al.</em>, 2006&lt;sup&gt;207&lt;/sup&gt;</td>
<td>Population not relevant</td>
</tr>
<tr>
<td>Gomez-castillo &amp; Bennett, 2005&lt;sup&gt;208&lt;/sup&gt;</td>
<td>Overseas cost study</td>
</tr>
<tr>
<td>Guo <em>et al.</em>, 2003&lt;sup&gt;209&lt;/sup&gt;</td>
<td>Further report of study already included</td>
</tr>
<tr>
<td>Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé, 2001&lt;sup&gt;10&lt;/sup&gt;</td>
<td>No cost data</td>
</tr>
<tr>
<td>Mutschler &amp; Muth, 2001&lt;sup&gt;210&lt;/sup&gt;</td>
<td>Article in German</td>
</tr>
<tr>
<td>Heng <em>et al.</em>, 2000&lt;sup&gt;211&lt;/sup&gt;</td>
<td>Intervention not relevant</td>
</tr>
<tr>
<td>Mitton &amp; Hailey, 1999&lt;sup&gt;212&lt;/sup&gt;</td>
<td>Cost and effectiveness not considered together</td>
</tr>
<tr>
<td>Mason <em>et al.</em>, 1999&lt;sup&gt;213&lt;/sup&gt;</td>
<td>Cost and effectiveness not considered together</td>
</tr>
<tr>
<td>Tibbles &amp; Edelsberg, 1996&lt;sup&gt;214&lt;/sup&gt;</td>
<td>Discursive article</td>
</tr>
</tbody>
</table>
### Appendix 7  Ongoing clinical trials

Hyperbaric oxygen therapy - ongoing trials (7 January 2008)

<table>
<thead>
<tr>
<th>Site</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>International</strong></td>
<td><strong>Ongoing/recruiting:</strong></td>
</tr>
</tbody>
</table>
| International Clinical Trials Registry Platform Portal - WHO  
http://www.who.int/ictrp/search/en/index.html | Hyperbaric Oxygen in Lower Limb Trauma  
| | Hyperbaric Oxygen Treatment in Patients With White Matter Hyperintensities  
http://clinicaltrials.gov/show/NCT00497432 |
| | Dose Escalation Study of Hyperbaric Oxygen With Radiation and Chemotherapy to Treat Squamous Cell Carcinoma of the Head and Neck  
http://clinicaltrials.gov/show/NCT00474825 |
| | Hyperbaric Oxygen Therapy and Angiogenesis in Diabetic Patients With Foot Ulcers  
http://clinicaltrials.gov/show/NCT00475202 |
| | One versus Three Hyperbaric Oxygen Treatments for Acute Carbon Monoxide Poisoning  
http://clinicaltrials.gov/show/NCT00465855 |
| | Randomized Controlled Trial of Hyperbaric Oxygen in Patients Who Have Taken Bisphosphonates  
http://clinicaltrials.gov/show/NCT00462098 |
| | Effects of Hyperbaric Oxygen Therapy on Children With Autism  
http://clinicaltrials.gov/show/NCT00406159 |
| | Effects of Hyperbaric Oxygenation Therapy on Adaptive, Aberrant and Stereotyped Behaviors in Children With Autism  
http://clinicaltrials.gov/show/NCT00404846 |
| | Prevention of Radiotherapy Side-Effects by Early Hyperbaric Oxygen Administration  
http://www.controlled-trials.com/ISRCTN25123615 |
| | An Evaluation of Hyperbaric Treatments for Children With Cerebral Palsy  
http://clinicaltrials.gov/show/NCT00290186 |
| | Hyperbaric Oxygen in Lower Leg Trauma  
http://clinicaltrials.gov/show/NCT00264511 |
| | Study to Determine if Hyperbaric Oxygen Therapy is Helpful for Treating Radiation Tissue Injuries  
http://clinicaltrials.gov/show/NCT00134628 |
| | Randomised Phase II Trial of Hyperbaric Oxygen Therapy in Patients With Chronic Arm Lymphoedema After Radiotherapy for Early Breast Cancer  
http://www.controlled-trials.com/ISRCTN00743708 |
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<th>Site</th>
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</thead>
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<td><strong>International</strong></td>
<td>Hyperbaric Oxygen Therapy in Treating Patients With Radiation Necrosis of the Brain</td>
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<tr>
<td></td>
<td><a href="http://clinicaltrials.gov/show/NCT00087815">http://clinicaltrials.gov/show/NCT00087815</a></td>
</tr>
<tr>
<td></td>
<td>Hyperbaric Oxygen Therapy Compared With Standard Therapy in Treating Chronic Arm Lymphedema in Patients Who Have Undergone Radiation Therapy for Cancer</td>
</tr>
<tr>
<td></td>
<td><a href="http://clinicaltrials.gov/show/NCT00077090">http://clinicaltrials.gov/show/NCT00077090</a></td>
</tr>
<tr>
<td></td>
<td>Radiation Therapy Plus Hyperbaric Oxygen in Treating Patients With Newly Diagnosed Glioblastoma Multiforme</td>
</tr>
<tr>
<td></td>
<td><a href="http://clinicaltrials.gov/show/NCT00006460">http://clinicaltrials.gov/show/NCT00006460</a></td>
</tr>
<tr>
<td></td>
<td><strong>Completed:</strong></td>
</tr>
<tr>
<td></td>
<td><a href="http://clinicaltrials.gov/show/NCT00463671">http://clinicaltrials.gov/show/NCT00463671</a></td>
</tr>
<tr>
<td></td>
<td>Slowing the Degenerative Process, Long Lasting Effect of Hyperbaric Oxygen Therapy in Retinitis Pigmentosa</td>
</tr>
<tr>
<td></td>
<td><a href="http://clinicaltrials.gov/show/NCT00461435">http://clinicaltrials.gov/show/NCT00461435</a></td>
</tr>
<tr>
<td></td>
<td>A Phase I Clinical Trial of Hyperbaric Oxygen Combined With Radiation and Chemotherapy for Locally Advanced Squamous Cell Carcinoma of the Head and Neck</td>
</tr>
<tr>
<td></td>
<td><a href="http://www.controlled-trials.com/ISRCTN12244200">http://www.controlled-trials.com/ISRCTN12244200</a></td>
</tr>
<tr>
<td></td>
<td>Effects of Hyperbaric Oxygen Therapy in Autistic Children: A Pilot Study</td>
</tr>
<tr>
<td></td>
<td><a href="http://clinicaltrials.gov/show/NCT00324909">http://clinicaltrials.gov/show/NCT00324909</a></td>
</tr>
<tr>
<td></td>
<td>Double-blind Randomized Placebo-controlled Clinical Trial for Treatment of Breast Symptoms With Hyperbaric Oxygen After Breast-Preserving Operation and Radiation</td>
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<td></td>
<td><a href="http://www.controlled-trials.com/ISRCTN43727802">http://www.controlled-trials.com/ISRCTN43727802</a></td>
</tr>
<tr>
<td></td>
<td>Hyperbaric Oxygen Radiation Tissue Injury Study - IV</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>A Phase III, Multicentre, Single Blind, Randomised Controlled Trial in the Use of Hyperbaric Oxygen Therapy Versus Biofeedback Therapy in Patients With Chronic Faecal Incontinence Associated With Pudendal Neuropathy</td>
</tr>
<tr>
<td></td>
<td><a href="http://www.controlled-trials.com/ISRCTN8557959">http://www.controlled-trials.com/ISRCTN8557959</a></td>
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<tr>
<td></td>
<td>A Randomised Controlled Pilot Study in the Use of Hyperbaric Oxygen Therapy Versus Metronidazole in Chronic Pouchitis</td>
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<td><a href="http://www.controlled-trials.com/ISRCTN83399182">http://www.controlled-trials.com/ISRCTN83399182</a></td>
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<td>Efficacy of Hyperbaric Oxygen Therapy in Laryngectomy Patients</td>
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<td></td>
<td><a href="http://clinicaltrials.gov/show/NCT00026975">http://clinicaltrials.gov/show/NCT00026975</a></td>
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</tbody>
</table>

**Trials Central**

http://www.trialscentral.org/

No results

**Current Controlled Trials**

http://www.controlled-trials.com/

Hyperbaric Therapy and Deep Chemical Peeling

http://www.controlled-trials.com/mrct/trial/255047/hyperbaric+oxygen
<table>
<thead>
<tr>
<th>Site</th>
<th>Results</th>
</tr>
</thead>
</table>
| National Research Register http://www.nrr.nhs.uk/ | An Investigation into the Impact of Hyperbaric Oxygen Therapy on Quality of Life in Patients with Maxillofacial Soft Tissue- and Osteo-Radionecrosis  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0185139335  
Do we Give the Right Information to Hyperbaric Patients and Does it Help Them?  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0411176068  
Oxidative Effects of Hyperbaric Treatment.  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0183146319  
The Role of Hyperbaric Oxygen in the Success of Dental Implants for Jaw Resection in Cancer Patients  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0411167528  
The Influence of Surgical Restoration of Lower Limb Blood Flow and Hyperbaric Oxygen Therapy on Nerve Physiological Tests in Diabetic and Non-Diabetic Patients With Peripheral Vascular Disease  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0084078382  
Hyperbaric Oxygen Therapy and Myopia II  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0185139376  
Cochrane Neuromuscular Disease Review Group: Hyperbaric Oxygen for Treating Bell's Palsy (Idiopathic Facial Paralysis)  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0013091667  
The Relationship of Hyperbaric Oxygen Therapy and Angiogenesis Biomarkers in Diabetic Patients With Leg Ulcers  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0084029399  
A Pilot Study in the Use of Hyperbaric Oxygen in Chronic Proctitis Secondary to Ulcerative Colitis  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0084139687  
A Study to Assess the Effectiveness of Hyperbaric Oxygen in the Treatment of Complex Regional Pain Syndrome  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0185146415  
Double-Blind Randomised Phase II Study of Hyperbaric Oxygen in Patients With Radiation-Induced Brachial Plexopathy  
https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0258016781 |
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<td>The Effect of Hyperbaric Oxygen on Platelet Physiology and Inflammatory Protein Modifications <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N020313628">Link</a></td>
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<td>Evaluation on the Effects of Hyperbaric Oxygen Therapy <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0405128529">Link</a></td>
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<tr>
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<td>The Effect of Hyperbaric Oxygen Therapy on Diabetic Leg Ulcers: A Double Blind, Randomised-Controlled Trial <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0084096565">Link</a></td>
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<td>A Study of Hyperbaric Oxygen in Diabetes <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0405038016">Link</a></td>
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<td>The Influence of Hyperbaric Oxygen Therapy on the Clinical Course of Radiation Cystitis <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0411167313">Link</a></td>
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<td>Evaluation on the Effects of Hyperbaric Oxygen Therapy (HBO) <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0411175986">Link</a></td>
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<td>Hyperbaric Oxygen and Haematopoietic Stem Cell Mobilisation in Liver Disease <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0519198881">Link</a></td>
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<td>Induction of Neo-Vascularisation and Potentiation of Chemotherapy by Hyperbaric Oxygen in Patients with Large Breast Cancers (&gt;5cm) <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0470079743">Link</a></td>
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<td>Does Hyperbaric Oxygen Have a Role to Play in the Treatment of Chronic Anal Fissure? A Pilot Study <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0084105613">Link</a></td>
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<td></td>
<td>Setting up of Patient Database for Publication and Evaluation of Scientific Data Including HBO Results <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0265006742">Link</a></td>
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<td>Co-Ordinated Investigation into the Possible Long Term Health Effects of Diving <a href="https://portal.nihr.ac.uk/Profiles/NRR.aspx?Publication_ID=N0411051145">Link</a></td>
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<td>Site</td>
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<td>UK</td>
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</table>
COST B14 (Evaluation of Hyperbaric Oxygen Therapy for a Range of Conditions) http://www.oxynet.org/ProtocolsIndex.htm |
11 Glossary

11 Glossary

acute coronary syndrome (ACS)
A collective term for the spectrum of acute coronary disease associated with myocardial ischaemia. Clinical presentations recognised within this definition include unstable angina, non-ST elevation myocardial infarction and ST elevation myocardial infarction.

ADL
Activities of daily living.

AETMIS
Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé.

AGE
Arterial gas embolism.

AHRQ
Agency for Healthcare Research and Quality.

anaemia
Reduction in the concentration of erythrocytes or haemoglobin in the blood.

ATA
Atmosphere absolute.

AUD
Australian dollars.

autonomic
Self-controlling and functionally independent.

barotrauma
An injury that results from rapid or extreme changes in pressure.

Bell's palsy
A condition that results in paralysis of one side of the face.

bias
In general, any factor that distorts the true nature of an event or observation. In clinical investigations, a bias is any systematic factor other than the intervention of interest that affects the magnitude of (ie tends to increase or decrease) an observed difference in the outcomes of a treatment group and a control group. Bias diminishes the accuracy (though not necessarily the precision) of an observation. Randomisation is a technique used to decrease this form of bias. Bias also refers to a prejudiced or partial viewpoint that would affect someone's interpretation of a problem. Double blinding is a technique used to decrease this type of bias.

CADTH
Canadian Agency for Drugs and Technologies in Health.

caisson
Enclosed unit under high atmospheric pressure to keep out surrounding water.

calciphylaxis
Sudden local calcification of small arteries leading to painful ischaemia and ulceration caused by a hypersensitivity reaction to a challenging agent. Also known as calcific uraemic arteriolopathy.

cardiac neural regulation dysfunction
Disorder in the parasympathetic and sympathetic regulation of heart rate.

cardiopulmonary bypass
A procedure which allows a pump to temporarily assume the function of a patient’s heart and lungs during surgery, maintaining the circulation of the blood and oxygen content of the body.

CD18
A human gene.

cerebral arterial gas embolism (CAGE)
Gas bubbles traveling and lodging (embolising) in the arteries that supply the brain with blood (and oxygen).

cerebral oedema
Excess accumulation of water in the brain.

cerebrovascular accident
Sudden disruption of the blood supply to the brain causing a stroke.

crohn's disease
A condition which can affect any part of the gastrointestinal tract causing inflammation and ulceration.

clinical effectiveness
The extent to which a specific intervention, procedure, regimen, or service does what it is intended to do under ordinary circumstances, rather than controlled conditions. Or more specifically, the evaluation of benefit to risk of an intervention, in a standard clinical setting, using outcomes measuring issues of importance to patients (eg ability to do daily activities, longer life, etc).

clostridial myonecrosis
An infection of the soft tissue caused by the clostridium bacteria; also known as gas gangrene.

cluster headache
A recurring excruciating pain in one side of the head which begins quickly and is short lived.

CO
Carbon monoxide.

complex regional pain syndrome (CRPS)
Pain and swelling in one part of the body. Any part of the body can be affected but the hands, feet, elbows or knees are the most usual.

composite graft
Replacement of a faulty part of the body with several structures such as skin and cartilage.
confidence interval (CI)
Depicts the range of uncertainty about an estimate of a treatment effect. It is calculated from the observed differences in outcomes of the treatment and control groups and the sample size of a study. The confidence interval (CI) is the range of values above and below the point estimate that is likely to include the true value of the treatment effect. The use of CIs assumes that a study provides one sample of observations out of many possible samples that would be derived if the study were repeated many times. Investigators typically use CIs of 90%, 95%, or 99%. For instance, a 95% CI indicates that there is a 95% probability that the CI calculated from a particular study includes the true value of a treatment effect. If the interval includes a null treatment effect (usually 0.0, but 1.0 if the treatment effect is calculated as an odds ratio or relative risk), the null hypothesis of no true treatment effect cannot be rejected.

cost effectiveness
A comparison of alternative interventions in which costs are measured in monetary units and outcomes are measured in non-monetary units, eg reduced mortality or morbidity.

cystitis
Inflammation of the bladder often caused by infection.

decompression illness
A syndrome occurring after returning from high to normal atmospheric pressure caused by nitrogen dissolved in the blood stream expanding to cause bubbles which block circulation in small blood vessels.

DOMS
Delayed onset muscle soreness.

DORCTHIM
Database of RCTs in Diving and Hyperbaric Medicine.

double blind
Neither the participants in a trial nor the investigators (outcome assessors) are aware of which intervention the participants are given. The purpose of blinding the participants (recipients and providers of care) is to prevent performance bias. The purpose of blinding the investigators (outcome assessors, who might also be the care providers) is to protect against detection bias.

EDSS
Expanded Disability Status Scale.

electrocardiogram (ECG)
A diagnostic test that monitors the electrical activity of the heart.

enteritis
Inflammation of the small intestine.

fibromyalgia
A chronic condition that causes fatigue, pain in the muscles and ligaments and tenderness in certain parts of the body.

FSS
Functional Status Scores.

gas embolism
A bubble of gas, such as nitrogen or air, lodged in a blood vessel.

GRA
Global Response Assessment.

grey literature
Research reports and other literature in print and electronic formats that is not found in traditional peer-reviewed publications or otherwise controlled by commercial publishers. Examples are government agency monographs, symposium proceedings, and industry reports.

HAD
Hospital Anxiety Depression scale.

HBV
Hepatitis B virus.

health technology assessment (HTA)
The systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.

HEED
Health Economics Evaluation Database.

heliox
A breathing gas composed of helium and oxygen used in medicine and diving at great depths.

hepatectomy
Surgical removal of the liver.

hepatitis
Inflammation of the liver.

heterogeneity
In meta-analysis heterogeneity refers to variability or differences in the estimates of effects among studies. A distinction is sometimes made between “statistical heterogeneity” (differences in the reported effects), “methodological heterogeneity” (differences in study design) and “clinical heterogeneity” (differences between studies in key characteristics of the participants, interventions or outcome measures). Statistical tests of heterogeneity are used to assess whether the observed variability in study results (effect sizes) is greater than that expected to occur by chance. However, these tests have low statistical power.

HF
High-frequency power.
HI
Headache index.

HORTIS
Hyperbaric Oxygen Radiation Tissue Injury Study.

HSE
Health and Safety Executive.

hyperbaric chamber
A sealable unit which artificially recreates pressures above normal atmospheric pressures.

hyperbaric oxygen therapy (HBOT)
A technique for exposing a patient to oxygen at high pressure used for the treatment of certain medical conditions including decompression illness.

hypoxia
A condition associated with a deficiency of oxygen in inhaled gases or in arterial blood and/or in the tissues.

iatrogenic
Resulting from the procedure.

incremental cost-effectiveness ratio (ICER)
Incremental cost-effectiveness ratio. The additional cost of the more expensive intervention as compared with the less expensive intervention divided by the difference in effect or patient outcome between the interventions, eg additional cost per QALY.

ICP
Intracranial pressure.

ICSI
Interstitial cystitis symptoms index.

intracranial
Within the skull.

ischaemia
Reduced blood flow usually because of blockage or narrowing of an artery.

iv
Intravenous.

IWGDF

keratoendotheliosis
An eye condition affecting the cells lining the cornea.

kPa
Kilopascal.

LF
Low-frequency power.

livedoid vasculopathy
A disease characterised by ulceration of the lower extremities.

lymphoma
A malignant tumour of the lymph nodes.

MACE
Major adverse coronary events.

malignant
Cancerous. Such tumours can invade and destroy surrounding tissue and have the capacity to spread. A tumour which is the result of such spread is known as ‘secondary’ or ‘metastatic’.

meta-analysis
Systematic methods that use statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome. This combination may produce a stronger conclusion than can be provided by any individual study. (Also known as data synthesis or quantitative overview.)

monoplace
Refers to a hyperbaric chamber which accommodates a single patient. The entire chamber is pressurised with 100% oxygen which the patient breathes directly.

MSAC
Medicare Services Advisory Committee.

multiplace
Refers to a hyperbaric chamber which can accommodate more than one patient, observers and support personnel. It is pressurised with compressed air and the patient breathes 100% oxygen through a mask, head tent or endotracheal tube.

multiple sclerosis (MS)
A chronic degenerative condition which affects the central nervous system.

myocardial infarction (MI)
Damage that occurs to the heart muscle when the oxygen supply is disrupted.

NOBT
Normobaric oxygen.

necrosis
Cell death caused by disease, injury or interference with blood supply.

necrotising faciitis
A bacterial infection of the membranous layer of connective tissue beneath the skin by Streptococcus Type A. There is tissue necrosis and toxin production causing shock and organ failure.

neoadjuvant
Refers to chemotherapy given before the treatment of a primary tumour with the aim of improving the results of surgery or radiotherapy and preventing metastases.
**neuroblastoma**
A malignant tumour composed of embryonic nerve cells.

**neuropathy**
Disease of the peripheral nerves which usually causes weakness and numbness.

**neuropsychometric dysfunction**
Inability of the brain to carry out certain cognitive tasks.

**neutrophil**
A type of white blood cell.

**NHMRC**
National Health and Medical Research Council.

**NHS**
National Health Service.

**NHS EED**
NHS Economic Evaluation Database.

**NHS Quality Improvement Scotland (NHS QIS)**
NHS QIS has been established to lead in improving the quality of care and treatment delivered by NHSScotland. To do this, it sets standards and monitors performance, and provides NHSScotland with advice, guidance and support on effective clinical practice and service improvements.

**NIHSS**
National Institute of Health Stroke Scale.

**number needed to treat (NNT)**
A measure of treatment effect that provides the number of patients who need to be treated to prevent one outcome event. It is the inverse of absolute risk reduction (1 ÷ absolute risk reduction), ie 1.0 ÷ (Pc - Pt). For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the number needed to treat would be 1.0 ÷ (0.25 - 0.10) = 6.7 patients.

**normobaric**
Pressure equivalent to that at sea level.

**NSAID**
Non-steroidal anti-inflammatory drug.

**O₂**
Oxygen.

**OR**
Odds ratio.

**orthopaedic**
Refers to the branch of surgery concerned with correcting deformities caused by disease of or damage to the bones and joints of the skeleton.

**osteomyelitis**
Acute or chronic infection of the bone or bone marrow.

**osteonecrosis**
Condition resulting from poor blood supply to an area of bone causing bone death.

**osteoradionecrosis (ORN)**
Bone death following damage by radiation.

**otitis externa**
Condition causing inflammation of the external ear canal.

**PBT**
Pulmonary barotrauma.

**PEDIS**
Perfusion, extent, depth, infection, severity and sensation.

**peridontitis**
Inflammatory diseases affecting the tissues that surround and support the teeth.

**peripheral obstructive arterial disease**
Narrowing of the arteries most commonly in the legs due to the build up of fatty deposits, causing impaired blood flow.

**placebo**
An inactive substance or treatment given to satisfy a patient’s expectation for treatment. In some controlled trials (particularly investigations of drug treatments) placebos that are made to be indistinguishable by patients (and providers when possible) from the true intervention are given to the control group to be used as a comparative basis for determining the effect of the investigational treatment.

**pneumatosis cystoides intestinalis**
A condition characterised by the presence of thin-walled, gas-containing cysts in the wall of the intestines.

**polymorphonuclear leukocyte**
A type of white blood cell.

**post-anoxic encephalopathy**
Degenerative disease of the brain following a lack of oxygen.

**primary literature**
Reports ‘original research’ in which data are first collected. The term is sometimes used to distinguish it from ‘secondary research’, meta-analysis and other ways of combining studies (such as economic analysis and decision analysis). However, because systematic reviews can provide answers not possible from individual studies they can also be considered to be primary research.

**proctitis**
Inflammation of the rectum.

**prophylactic**
Refers to drugs given to prevent an unwanted outcome.

**PTA**
Pure tone average.
quality of life (QoL)
Patient outcome measures that extend beyond traditional measures of mortality and morbidity, to include such dimensions as physiology, function, social activity, cognition, emotion, sleep and rest, energy and vitality, health perception, and general life satisfaction. (Some of these are also known as health status, functional status, or quality of life measures).

randomised controlled trial (RCT)
An experiment of two or more interventions in which eligible people are allocated to an intervention by randomisation. The use of randomisation then permits the valid use of a variety of statistical methods to compare outcomes of the interventions.

recompression
Controlled gradual return to normal pressure.

retinitis pigmentosa
Hereditary eye disorder.

relative risk (RR)
The ratio of (statistical) risk in the intervention group to the risk in the control group. A relative risk of one indicates no difference between comparison groups. For undesirable outcomes an RR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.

SCI
Science citation index.

SCUBA
Self-contained underwater breathing apparatus.

SD
Standard deviation of the mean.

secondary literature
Reports research that does not generate primary data but that involves the qualitative or quantitative synthesis of information from multiple primary studies. Examples are literature reviews, meta-analyses, decision analyses and consensus statements.

sensitivity analysis
A means to determine the robustness of a mathematical model or analysis (such as a cost-effectiveness analysis or decision analysis) that tests a plausible range of estimates of key independent variables (eg costs, outcomes, probabilities of events) to determine if such variations make meaningful changes to the results of the analysis. Sensitivity analysis also can be performed for other types of study: eg clinical trials analysis (to see if inclusion/exclusion of certain data changes results) and meta-analysis (to see if inclusion/exclusion of certain studies changes results).

sham
A dummy medication, treatment or procedure.

SIGN
Scottish Intercollegiate Guidelines Network.

SRS
Stereotactic radiosurgery.

SSI
Surgical site infection.

STRI
Soft tissue radiation injury.

stroke
When the blood supply to the brain is cut off, the cells become damaged or die due to lack of oxygen.

systematic review/overview
A form of structured literature review that addresses a question that is formulated to be answered by analysis of evidence, and involves objective means of searching the literature, applying predetermined inclusion and exclusion criteria to this literature, critically appraising the relevant literature, and extraction and synthesis of data from evidence base to formulate findings. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

TBI
Traumatic brain injury.

thrombomodulin
A protein molecule attached to the membrane on the surface of endothelial cells.

UHMS
Undersea and Hyperbaric Medical Society.

UK
United Kingdom.

urology
Branch of medicine pertaining to diseases of the urinary and genital apparatus.

USA
United States of America.

USAF
United States Air Force.

vagotonic
Relating to hyperexcitability of the vagus nerve.

VAS
Visual analogue scale.

weighted mean difference (WMD)
A method of meta-analysis used to combine measures on continuous scales (such as weight), where the mean, standard deviation and sample size in each group are known. The weight given to each study (eg how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect and, in the statistical software in RevMan and CDSR, is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.
X-ray
An imaging technique that uses beams of penetrating electromagnetic energy.
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