Hyperbaric oxygen therapy for the treatment of non-healing, refractory wounds in non-diabetic patients and refractory soft tissue radiation injuries

May 2003

MSAC application 1054

Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Australian Government Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Elmer Villanueva, Associate Professor Anthony Harris, Ms Emily Petherick, Dr Renea Johnston and Ms Alexandra Raulli, from the Centre for Clinical Effectiveness, Monash Institute of Health Services Research and Centre for Health Economics, Monash University and Edited by Dr Alana Mitchell, ScienceLink Pty Ltd. The report was endorsed by the Australian Government Minister for Health and Ageing on 31

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***MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.***

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# Executive summary

## The procedure

Hyperbaric oxygen therapy (HBOT) involves the intermittent inhalation of 100 per cent oxygen in chambers pressurised above one atmosphere absolute. Depending on the reason for HBOT, the duration of treatment session varies from 45 to 300 minutes, although times of 90 to 120 minutes are most common, for a variable number of sessions.

This report evaluates the safety, effectiveness, and cost-effectiveness of HBOT in the management of non-healing wounds in non-diabetic patients and in refractory soft tissue radiation injuries.

## Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Institute of Health Services Research and the Health Economics Unit, Monash University, was engaged to conduct a systematic review of literature on hyperbaric oxygen therapy for treatment of refractory soft tissue radiation injuries and non-healing wounds in non-diabetic patients. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

**MSAC’s assessment of hyperbaric oxygen therapy for the treatment of non-healing wounds in non-diabetic patients and refractory soft tissue radiation injuries**

## Clinical need

Hyperbaric oxygen therapy is an established therapeutic modality in a number of indications. As stated in a previous report (MSAC 2001), there are no reliable Australian estimates for the prevalence of soft-tissue radiation injuries and non-healing wounds in non-diabetic patients.

Data presented at the 10th annual scientific meeting of the Hyperbaric Technicians and Nurses Association and the Australian and New Zealand Hyperbaric Medicine Group (Christchurch, 29-31 August, 2002) showed that 1,236 patients underwent 21,033 episodes of HBOT in Australia from 1 July 2001 to 30 June 2002. Of these, 120 patients (9.7%) were treated for soft tissue radiation injuries and 166 patients (13.4%) were treated for hypoxic, non-diabetic wounds.

## Safety

Estimates collected through national registries of the incidence of adverse events relating to HBOT suggested that most were self-limited and resolved after termination of

therapy. As was presented in the previous report (MSAC 2001), the most common forms of adverse events were myopia, barotrauma, claustrophobia and oxygen toxicity. Serious, life-threatening events and fatalities were rare.

## Effectiveness

Twenty one studies were included in the assessment of the effectiveness of HBOT, five examining non-healing wounds in non-diabetic patients and 16 dealing with refractory soft tissue radiation injuries. Although evidence in support of the effectiveness of HBOT in both indications includes higher level study designs such as randomised controlled trials (RCTs) and non-randomised controlled studies, it was of low methodological quality, failing to meet relevant validity criteria.

Furthermore, the majority of studies reported end-points of uncertain clinical significance or patient relevance. Relevant outcomes including healing of wounds were sometimes reported, however the validity of assessment of these outcomes was uncertain due to a lack of objective or blinded assessment, and failure to explicitly report measurement criteria.

Twelve case series (three reporting on non-healing, refractory wounds in non-diabetic patients and nine on refractory soft tissue radiation injuries) were identified that enrolled consecutive patients. The non-comparative nature of such studies limited the use of the information contained in the case series due to the considerable potential for bias inherent in such designs. Nevertheless, such studies were used to supplement the evidence available from comparative studies.

## Non-healing wounds in non-diabetic patients

Two controlled studies met the entry criteria. One RCT showed a decrease in wound area and a comparative study using historical controls showed trends toward the prevention of wound breakdown and infection as well as reductions in length of hospitalisation.

## Refractory soft tissue radiation injuries

Six controlled studies met the inclusion criteria. Four RCTs examined four different sub- indications related to radiation therapy. A small RCT examining the use of HBOT for cognitive impairment following brain irradiation showed non-significant improvement in neuropsychological function. Another RCT evaluating HBOT for radiation-induced brachial plexopathy showed no significant differences in sensory thresholds or quality of life between those receiving HBOT and controls. In a group of patients at high risk for the development of osteoradionecrosis, HBOT was found to increase the likelihood of healing tooth socket wounds following extraction compared to the administration of penicillin. The remaining RCT showed that HBOT reduced the likelihood of major wound infection, major wound dehiscence and delayed wound healing in myocutaneous grafts in patients who had undergone radiation therapy.

## Cost-effectiveness

The clinical evidence was inadequate to substantiate claims that HBOT was cost- effective in the treatment of refractory soft tissue radiation injuries or non-diabetic refractory wounds. There was not evidence of sufficient quality to substantiate claims that it will either lead to an overall saving in resource use, or that it would lead to substantial patient relevant gains in health-related quality of life compared to current medical treatments at an acceptable cost.

## Recommendations

The clinical evidence was inadequate to substantiate claims that hyperbaric oxygen therapy (HBOT) was cost-effective in the treatment of refractory soft tissue radiation injuries or non-diabetic refractory wounds. However, MSAC recommended that, as there are no effective alternative therapies and in view of the progress of local data collections and an international trial, funding for HBOT continue for MBS listed indications at currently eligible sites, for a further three years.

- The Minister for Health and Ageing accepted this recommendation on 31 August 2004.

# Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the therapeutic use of hyperbaric oxygen therapy (HBOT) for non-healing wounds in non-diabetic patients and refractory soft tissue radiation injuries. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC’s terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for HBOT for the treatment of non-healing wounds in non-diabetic patients and refractory soft tissue radiation injuries.

# Background

**Hyperbaric oxygen therapy for the treatment of non-healing, refractory wounds in non-diabetic patients and refractory soft tissue radiation injuries**

## Previous evaluation

The Medical Services Advisory Committee has previously examined the effectiveness, safety, and cost-effectiveness of HBOT for a number of indications (MSAC 2001; Application 1018-1020). The previous report was endorsed by the Commonwealth Minister for Health and Aged Care on 9 February 2001.

The present report builds on the findings of this earlier publication. It is limited to the assessment of HBOT as last-line treatment of non-healing wounds in non-diabetic patients and refractory soft tissue radiation injuries. Some issues, such as descriptions of the procedure, general discussions of safety and primary studies previously identified as relating to the present indications remain unchanged. They are included here for completion.

## The procedure

Hyperbaric oxygen therapy involves the intermittent inhalation of pure oxygen in chambers pressurised above one atmosphere absolute (ATA). One ATA is defined as atmospheric pressure at sea level which is equivalent to 101.3 kiloPascals (kPa) or 14.7 pounds per square inch (psi).

Exposure to hyperbaric oxygen (HBO) is measured jointly by the pressures used in single-treatment exposures and the duration and number of treatment sessions. Tolerance to therapy is dependent on these parameters. In general, HBOT is well tolerated if pressures do not exceed three ATA and the treatment session lasts less than two hours. Depending on the reason for HBOT, treatment duration can vary from 45 to

300 minutes, although most treatments last from 90 to 120 minutes, for a variable number of sessions.

Hyperbaric oxygen therapy is administered in two types of chambers – monoplace and multiplace. A monoplace chamber accommodates one patient and is the most common type used worldwide. It can be pressurised with either pure oxygen or air. In the latter case, oxygen is delivered to the patient via a mask, hood or endotracheal tube. The smaller size of the chamber provides relative portability and lower cost, but imposes limits on ready access to the patient. The risk of fire is increased in the event that pure oxygen is used to pressurise the chamber.

Multiplace chambers can accommodate several occupants, including observers and medical and support personnel. The multiplace chamber is pressurised with air instead of

100 per cent oxygen and subjects undergoing therapy breathe pure oxygen through masks, hoods, or endotracheal tubes. The chamber’s larger size allows personnel to enter and move about with relative ease in order to deal with acute problems. The risk of fire is also reduced by administration of pure oxygen through patient-specific devices.

The previous report on HBOT (MSAC 2001) noted that there were marked regional variations in the delivery systems used. Australian clinical practice and expertise is primarily with multiplace chambers which are generally used by the majority of established hyperbaric facilities. In contrast, many facilities in the United States, including those used for intensive care patients, are solely equipped with monoplace chambers (MSAC 2001).

According to expert clinical opinion, the therapeutic effect is the same regardless of the delivery system. As was the case for the previous report, no attempt has been made here to perform a comparative assessment of the two types of delivery systems. The higher pressures that multiplace chambers can deliver were considered irrelevant to the assessment as the majority of treatments are administered at less than three ATA (MSAC 2001).

# Intended purpose

The focus of the present report is the use of HBOT as last-line therapy for non-healing, refractory wounds in non-diabetic patients and for refractory soft tissue radiation injuries.

Hyperbaric oxygen is thought to influence the restorative course through the major process of wound healing, generally defined as the physiologic repair of injured tissue to obtain restoration of integrity (Mustoe & Porras-Reyes 1993). Oxygen insufficiency is a major component of the pathophysiology of many diseases. The rationale behind HBOT is that improved delivery of oxygen to the affected tissues will facilitate recovery from disease (NHLBI 1991).

Hyperbaric oxygen increases the partial pressure of oxygen in all tissues of the body (Hammarlund 1994). In turn, increased partial pressure of oxygen contributes to the enhancement of leukocyte-killing activity (Mader et al 1980), a decrease in white cell adherence to capillary walls (Zamboni et al 1993), vasoconstriction in normal vessels, restoration of fibroblast growth and collagen production (Meltzer & Myers 1986), neovascularisation (Knighton et al 1981) and preservation of adenosine triphosphate in the cell membrane, with secondary reduction in tissue oedema, modulation of selected immune responses (Bonomo et al 2000), and increased cellular proliferation (Hammarlund 1994, Boykin 1996).

Regardless of the specific type of wound, the natural reparative process has the following general sequence: haemostasis, inflammation, angiogenesis, collagen synthesis, epithelisation, and contraction (Hom et al 1995). Non-healing wounds result from interruption or delay in one or more steps in this sequence.

In contrast, radiation induces acute adverse effects on soft tissue through a number of pathways, including modification of the normal cellular environment (Mustoe & Porras- Reyes 1993), direct killing of epithelial and parenchymal cells, fibrosis of the interstitial medium (Hom et al 1995), decreased vascularity, hypoxia, and impairment of the proliferative capacities of local tissues. This renders tissues less able to respond to the inflammatory stimulus through the normal repair process. These cellular effects manifest as ulceration, oedema, and inflammation which are the epithelial and dermal changes characteristic of acute radiation injury (Mustoe & Porras-Reyes 1993).

Surgery in such tissues has an increased complication rate because the angiogenesis, fibroplasia and white cell activity required for wound healing are all compromised (Neovius et al 1997). Hyperbaric oxygen has been found to increase perfusion in irradiated tissues (Marx et al 1990) and induce fibroplasia and angiogenesis (Nemiroff et al 1985).

The physiologic action of HBOT on refractory soft tissue radiation injuries and non- healing wounds was established in experimental studies of wound healing. The benefit of HBOT in clinical settings is unclear and is the focus of the present report.

## Burden of disease

As stated in the previous report of HBOT (MSAC 2001), there are no reliable Australian estimates for the prevalence of soft tissue radiation injuries and non-healing wounds in non-diabetic patients.

Data presented at the 10th annual scientific meeting of the Hyperbaric Technicians and Nurses Association and the Australian and New Zealand Hyperbaric Medicine Group (Christchurch, 2002 August 29-31) showed that 1,236 patients underwent 21,033 episodes of HBOT in Australia from 1 July 2001 to 30 June 2002. Of these, 120 patients (9.7%) were treated for soft tissue radiation injuries and 166 patients (13.4%) were treated for hypoxic, non-diabetic wounds (HTNA and ANZHMG 2002).

## Existing procedures and comparators

In this review, the use of HBOT was compared to procedures that did not use HBOT, including standard or conventional therapy (variously defined), normobaric oxygen or placebo procedures. As discussed more fully under Approach to Assessment, we included all studies with HBOT as a primary therapy and employing a direct, head-to- head comparison, regardless of the nature of the comparator.

## Marketing status of the device/technology

A large number of monoplace units are listed on the Australian Register of Therapeutic

Goods. Multiplace chambers, if fixed installations, are exempt from listing.

## Current reimbursement arrangement

Interim funding for hyperbaric oxygen therapy for the indications considered in this report is currently listed in the Medicare Benefits Schedule (MBS):

**13015**: HYPERBARIC OXYGEN THERAPY for treatment of soft tissue radionecrosis or chronic non-diabetic wounds where hypoxia can be demonstrated performed in a comprehensive hyperbaric medicine facility, under the supervision of a medical practitioner qualified in hyperbaric medicine for a period in the hyperbaric chamber between 1 hour 30 minutes and 3 hours including any associated attendance

In addition, HBOT is currently funded for a range of other indications (MBS Items

13020, 13025, 13030), which may be related to those presented in the current report.

Medicare item number 13020 is used to reimburse HBOT for treatment of decompression illness, gas gangrene, air or gas embolism; diabetic wounds including diabetic gangrene and diabetic foot ulcers; necrotising soft tissue infections including necrotising fasciitis, Fournier's gangrene and for the prevention and treatment of osteoradionecrosis.

All MBS entries are described in Table 1. No breakdown of these claims by indication was available from the Health Insurance Commission.

**Table 1 Medicare Benefits Schedule item numbers and descriptions for hyperbaric oxygen therapy services**

|  |  |
| --- | --- |
| **Item Number** | **Description** |
| **13015** | HYPERBARIC OXYGEN THERAPY for treatment of soft tissue radionecrosis or chronic non-diabetic wounds where hypoxia can be demonstrated performed in a comprehensive hyperbaric medicine facility, under the supervision of a medical practitioner qualified in hyperbaric medicine for a period in the hyperbaric chamber between 1 hour 30 minutes and 3 hours including any associated attendance. Fee: $206.55 |
| **13020** | HYPERBARIC OXYGEN THERAPY for treatment of decompression illness, gas gangrene, air or gas embolism; diabetic wounds including diabetic gangrene and diabetic foot ulcers; necrotising soft tissue infections including necrotising fasciitis, Fournier's gangrene or for the prevention and treatment of osteoradionecrosis, performed in a comprehensive hyperbaric medicine facility, under the supervision of a medical practitioner qualified in hyperbaric medicine, for a period in the hyperbaric chamber of between 1 hour 30 minutes and 3 hours, including any associated attendance. Fee: $209.80 |
| **13025** | HYPERBARIC OXYGEN THERAPY for treatment of decompression illness, air or gas embolism, performed in a comprehensive hyperbaric medicine facility, under the supervision of a medical practitioner qualified in hyperbaric medicine, for a period in the chamber greater than 3 hours, including and associated attendance  - per hour (or part of an hour). Fee: $93.85 |
| **13030** | HYPERBARIC OXYGEN THERAPY performed in a comprehensive hyperbaric medicine facility where the medical practitioner is pressurised in the hyperbaric chamber for the purpose of providing continuous life saving emergency treatment, including any associated attendance - per hour (or part of an hour) Fee:  $132.55 |

The number of services under each of the MBS entries is given by State and calendar year in Tables 2 to 5.

**Table 2 Number of services claimed for MBS Item 13015, by state and calendar year**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Calendar year** | **Number of services by State** | | | | | | | | **Total number of services** |
| **NSW** | **Vic** | **Qld** | **SA** | **WA** | **Tas** | **ACT** | **NT** |
| 2001 | 61 | 69 | 124 | 0 | 0 | 8 | 0 | 0 | 262 |
| 2002 | 893 | 1,900 | 1,866 | 21 | 20 | 160 | 0 | 0 | 4,860 |
| 2001 and 2002 combined | 954 | 1,969 | 1,990 | 21 | 20 | 168 | 0 | 0 | 5,122 |
| 2002 (services per 10,000 populationa) | (1.34) | (3.89) | (5.00) | (0.14) | (0.10) | (3.38) | (0.00) | (0.00) | (2.46) |

Data available at [www.hic.gov.au/providers/health\_statistics/index.htm](http://www.hic.gov.au/providers/health_statistics/index.htm)

a Rate per 10,000 population using the number of services in 2002 and State-specific population estimates from the Australian Bureau of

Statistics

**Table 3 Number of services claimed for MBS Item 13020, by State and calendar year**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Calendar year** | **Number of services by state** | | | | | | | | **Total number of services** |
| **NSW** | **Vic** | **Qld** | **SA** | **WA** | **Tas** | **ACT** | **NT** |
| 1997 | 823 | 297 | 89 | 335 | 409 | 490 | 0 | 0 | 2,443 |
| 1998 | 1,567 | 977 | 311 | 232 | 280 | 396 | 20 | 19 | 3,802 |
| 1999 | 1,982 | 1,540 | 1,678 | 211 | 332 | 540 | 147 | 10 | 6,440 |
| 2000 | 2,257 | 3,398 | 2,196 | 322 | 360 | 634 | 45 | 106 | 9,318 |
| 2001 | 2,467 | 3,090 | 2,315 | 168 | 114 | 618 | 129 | 38 | 8,939 |
| 2002 | 1,356 | 2,960 | 1,174 | 274 | 40 | 321 | 73 | 92 | 6,290 |
| 1997-2002a | 10,452 | 12,262 | 7,763 | 1,542 | 1,535 | 2,999 | 414 | 265 | 37,232 |
| 2002 (Services per 10,000 population)b | (2.04) | (6.06) | (3.15) | (1.80) | (0.21) | (6.78) | (2.27) | (4.65) | (3.19) |

Data available at [www.hic.gov.au/providers/health\_statistics/index.htm](http://www.hic.gov.au/providers/health_statistics/index.htm)

a Total number of services for 1997-2002

b Rate per 10,000 population using the number of services in 2002 and State-specific population estimates from the Australian Bureau of

Statistics

**Table 4 Number of services claimed for MBS Item 13025, by state and calendar year**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Calendar year** | **Number of services by state** | | | | | | | | **Total number of services** |
| **NSW** | **Vic** | **Qld** | **SA** | **WA** | **Tas** | **ACT** | **NT** |
| 1997 | 3 | 6 | 0 | 1 | 2 | 2 | 0 | 0 | 14 |
| 1998 | 5 | 3 | 2 | 4 | 0 | 2 | 0 | 0 | 16  10 |
| 1999 | 3 | 1 | 2 | 0 | 1 | 1 | 0 | 2 |
| 2000 | 4 | 12 | 1 | 0 | 3 | 1 | 0 | 0 | 21  30 |
| 2001 | 9 | 6 | 2 | 3 | 7 | 1 | 2 | 0 |
| 2002 | 14 | 6 | 9 | 0 | 2 | 1 | 0 | 0 | 32 |
| 1997-2002a | 38 | 34 | 16 | 8 | 15 | 8 | 2 | 2 | 123 |
| 2002 (Services per 10,000 population)b | (0.02) | (0.01) | (0.02) | (0.00) | (0.01) | (0.02) | (0.00) | (0.00) | (0.02) |

Data available at [www.hic.gov.au/providers/health\_statistics/index.htm](http://www.hic.gov.au/providers/health_statistics/index.htm)

a Total number of services for 1997-2002

b Rate per 10,000 population using the number of services in 2002 and State-specific population estimates from the Australian Bureau of

Statistics

**Table 5 Number of services claimed for MBS Item 13030, by state and calendar year**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Calendar year** | **Number of services by state** | | | | | | | | **Total number of services** |
| **NSW** | **Vic** | **Qld** | **SA** | **WA** | **Tas** | **ACT** | **NT** |
| 1997 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 1998 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1999 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2001 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| 2002 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1997-2002a | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 3 |

Data available at [www.hic.gov.au/providers/health\_statistics/index.htm](http://www.hic.gov.au/providers/health_statistics/index.htm)

a Total number of services for 1997-2002

# Approach to assessment

## Review of literature

The medical literature was searched to identify relevant studies and reviews published between 1966 and 2002 using the Ovid databases and specific Internet-based sites and search engines (Table 6).

**Table 6 Electronic databases used in this review**

|  |
| --- |
| **Database Period/Issue covered** |
| Cochrane Library including: Issue 4, 2002  The Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effectiveness (DARE) The Cochrane Controlled Trials Register (CCTR) |
| CINAHL (OVID) 1982 to October Week 4 2002 |
| Current Contents (OVID) 1993 Week 27 to 2002 Week 45 |
| Medline (OVID) 1966 to October Week 4 2002 |
| PreMedline (OVID) 30 October 2002 |
| Biological Abstracts (OVID) 1980 to September 2002 |
| ACP Journal Club (OVID) 1991 to September/October 2002 |
| EMBASE (OVID) 1966 to 12 November 2002 |
| [CancerLit (www.cancer.gov/search/cancer\_literature/)](http://www.cancer.gov/search/cancer_literature/)) 1993 to 2 December 2002 |
| National Guidelines Clearing House ([www.guideline.gov/)](http://www.guideline.gov/)) Searched on 13 January 2003 |
| HBO Evidence (www.hboevidence.com) Searched on 13 January 2003 |

The search terms used are shown in Table 7. The health technology assessment agency websites listed in Appendix E were also searched. Reference lists of publications were scanned and relevant citations retrieved. Publications recommended by the supporting committee and the applicant were also retrieved and assessed.

**Table 7 Search terms**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention** | **Indication 1**  **Soft tissue radiation injuries** | **Indication 2**  **Non-healing wounds in non-diabetic patients** | **Safety filter** | **Cost- effectiveness filterb** |
| Hyperbaric oxygenation[MeSH]  hyperbar$a  hbo$  multiplace chamber$  monoplace chamber$ | radiation injuries[MeSH] radiotherapy[MeSH] radiation sickness radiotherap$ radionecrosis$  radio$ necr$  soft tissue injuries[MeSH]  soft tissue$ | wounds and injuries[MeSH]  decubitus ulcer[MeSH]  leg ulcer[MeSH] skin ulcer[MeSH] foot ulcer[MeSH] sore$  ulcer$  wound$ | safety[MeSH]  intraoperative complications[MeSH]  postoperative complications[MeSH]  mortality[MeSH] complicat$ adverse event$ | economic$  cost$ |

a ‘$’ represent a series of letters at the end of a word segment (ie surg$). MeSH terms are indicated by ‘[MeSH]’ after the actual term (ie

neoplasia[MeSH])

b Search phrase construction involved appending the Boolean operator ‘OR’ for terms within a column. Across columns, the Boolean operator

‘AND’ was used

**Selection criteria**

The following criteria were developed *a priori* to determine eligibility of relevant studies, based on those used in the prior MSAC evaluation of HBOT (MSAC 2001) and refined iteratively.

**Subject characteristics**

Inclusions: non-diabetic patients with non-healing, refractory wounds who have failed conventional therapies; patients with soft tissue radiation injuries.

Exclusions: patients not diagnosed with either of the above conditions.

**Characteristics of the intervention**

Inclusions: HBOT in a monoplace or multiplace chamber.

**Characteristics of the comparison intervention**

Inclusions: procedures not using HBO, including standard or conventional therapy

(currently not defined), normobaric oxygen, or placebo procedures.

**Characteristics of the outcome**

Inclusions: all patient-relevant outcomes for both indications.

**Characteristics of the study design**

Inclusions: health technology assessments, systematic reviews, meta-analyses, and RCTs were sought initially. The search was extended to other controlled trials, cohort studies, and comparative studies. Case series were included if patients were enrolled consecutively or if all patients presenting within a specified time frame were included.

Exclusions: case series in non-consecutively selected patients, case reports, narrative reviews, abstracts, opinions.

**Characteristics of the publication**

Inclusions: studies in the English language, in addition to systematic reviews and RCTs published in any language.

Exclusions: non-systematic reviews or non-RCTs published in foreign languages.

**Search results**

**Non-healing wounds in non-diabetic patients**

The search strategy identified 1,009 articles. Based on a consideration of abstracts, 189 articles were ordered for full text assessment. One hundred and seventy-three of these were obtained by 20 February 2003 and assessed in full text. In addition, one case series (Cianci 1988; Appendix F3) was considered on expert advice that all patients within a specified time frame were enrolled. Of these 174 articles, five met the inclusion criteria.

Of the 168 articles that did not meet the primary inclusion criteria, three were animal studies, 16 were case reports, one did not use HBO as therapy, 75 were narrative reviews, eight did not use HBOT, 26 were not specific to the indication, 20 were opinion pieces, four were for topical oxygen therapy, and 15 did not have an appropriate patient spectrum.

**Refractory soft tissue radiation injuries**

The search strategy identified 793 articles. After abstracts were reviewed, 94 articles were ordered for full text assessment. Ninety-two of these were obtained by 20 February 2003 and assessed in full text. Of these 92 articles, 16 met the inclusion criteria. In addition, two case series (Bevers et al 1995, Lee et al 1994; Appendix F4) were considered on expert advice.

Of the 76 studies that did not meet the inclusion criteria, 15 were case reports, four did not use HBO as therapy, 21 were narrative reviews, three did not contain effectiveness data, five did not refer to soft tissue radiation injuries, five were opinion pieces, and 23 did not have an appropriate patient spectrum.

Following application of the selection criteria, the list of articles potentially eligible for further assessment was forwarded for review to the Supporting Committee which made further recommendations for inclusion.

**Data extraction**

Data were extracted using standardised instruments created for the assessment. Two reviewers examined each article and any discrepancies in evaluation were discussed and resolved through consensus. Attempts were made to contact the corresponding authors to clarify specific issues relating to validity or results, such as the consecutive enrolment of patients in case series.

**Assessment of validity**

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 8) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

**Table 8 Evidence dimensions**

|  |  |
| --- | --- |
| **Type of evidence** | **Definition** |
| Strength of the evidence  Level  Quality  Statistical precision | The study design used, as an indicator of the degree to which bias has been eliminated by designa  The methods used by investigators to minimise bias within a study design  The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect |
| Size of effect | The distance of the study estimate from the “null” value and the inclusion of only clinically important effects in the confidence interval |
| Relevance of evidence | The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used |

a See Table 9

Collectively, three sub-domains (level, quality and statistical precision) measure the strength of the evidence. The designations of the levels of evidence are shown in Table 9.

**Table 9 Designations of levels of evidencea**

|  |  |
| --- | --- |
| **Level of evidence** | **Study design** |
| I II  III-1  III-2  III-3  IV | Evidence obtained from a systematic review of all relevant randomised controlled trials  Evidence obtained from at least one properly-designed randomised controlled trial  Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)  Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group  Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group  Evidence obtained from case series, either post-test or pre-test/post-test |

a Modified from NHMRC (1999)

Critical appraisal refers to the process of evaluating the study design of included articles. The most rigorous study design for assessing the validity of therapeutic interventions is considered to be an RCT (Guyatt et al 1993, Sackett et al 2000).

**Assessment of primary studies**

The UK NHS Centre for Reviews and Dissemination assembled a list of criteria used for evaluating the validity of evidence from various study designs. The relevant validity criteria used in this review for assessing the quality of evidence are listed in Table 10.

Criteria to assess the validity of case series were based on those reported by the UK NHS Centre for Reviews and Dissemination, with some modifications in order to attain consensus among the reviewers on the final criteria.

**Table 10 Validity criteria according to study design**

|  |
| --- |
| **Study design Validity criteriaa** |
| RCT Randomised method  Allocation concealment  Blinding of patients, investigators and outcome assessors  Proportion lost to follow-up  Intention to treat analysis |
| Cohort Prospective/ retrospective  Comparable groups at inception  Identification and adjustment for confounding factors  Blind outcome assessment Sufficient duration of follow-up Proportion lost to follow-up |
| Case-control Explicit definition of cases  Adequate details of selection of controls  Comparable groups with respect to confounding factors  Interventions and other exposures assessed in same way for cases and controls  Appropriate statistical analysis |
| Case series Indication comparable across patients Disease severity comparable across patients Explicit entry criteria  Outcome assessed in all patients  Follow-up time uniform Outcomes assessed objectively Outcomes assessed in a blinded manner Outcome measures quantified |

a Modified from NHS Centre for Reviews and Dissemination

**Assessment of secondary studies**

The critical appraisal of systematic reviews was performed against the qualitative criteria (Chalmers & Altman 1995, Greenhalgh 1997, Sackett et al 2000) outlined in Table 11. These were designed to assess whether the systematic review was performed so as to minimise bias. The criteria assessed whether the systematic review contained explicit statements of the objectives and methods and whether the methods used were reproducible. Specific criteria assessed whether the review asked a focused question, if the eligibility criteria for included trials were explicit, what search strategy was used, how the validity of included trials was assessed and whether results of included trials were similar.

**Table 11 Validity criteria for appraisal of systematic reviews**

|  |
| --- |
| Is there a focused research question?  ie PICO elements: patient, intervention, comparator, outcomes |
| Are inclusion and exclusion criteria for selected studies stated? |
| Is there an explicit and comprehensive search strategy?  Did review incorporate a search strategy comprehensive enough that it was unlikely to have missed studies? |
| Are the included trials appraised for validity?  Are validity criteria stated? |
| Are results consistent from study to study?  Is homogeneity assessed? |

Adapted from Evidence Based Medicine Toolkit, University of Alberta [(www.med.ualberta.ca/ebm/ebm.htm)](http://www.med.ualberta.ca/ebm/ebm.htm))

**Data analysis**

Where statistical analysis was not provided in the original publication, the data were analysed for this assessment using Intercooled Stata 8.0 (College Station, Texas, USA).

**Expert advice**

A supporting committee with expertise in hyperbaric medicine, surgery, radiation oncology, general practice and consumer issues was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC’s practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided in Appendix B.

# Results of assessment

## Is it safe?

Table 12 presents the summary of a review of side effects observed following 21,033

HBOT episodes conducted in Australia between 1 July 2001 and 30 June 2002 for a variety of indications including those that are the focus of this review. The review revealed similar findings to those discussed previously (MSAC 2001).

**Table 12 Side effects associated with HBOT in Australia for financial year 2001-2002**

|  |
| --- |
| **Side effect Incidence per number of treatments** |
| Persistent ocular changes 1/112 (0.90%) |
| Significant ear barotrauma causing treatment interruption 1/170 (0.60%) |
| Claustrophobia 1/910 (0.10%) |
| CNS seizures (all treatment pressures) 1/1,548 (0.06%) |
| Sinus barotrauma 1/4,864 (0.02%) |
| Pulmonary oxygen toxicity 1/6,766 (0.01%) |
| Pulmonary barotrauma 0/15,475 (0.00%) |
| Deaths 0/21,033 (0.00%) |

Source: (HTNA and ANZHMG 2002)

The most common adverse events associated with the procedure were middle ear barotrauma and reversible myopia (Tibbles & Edelsberg 1996, Leach et al 1998). Other reported adverse events were oxygen toxicity and claustrophobia (MSAC 2001).

The previous report (MSAC 2001) noted that progressive myopia was associated with prolonged, daily exposure to HBO and was more common at higher pressures. However, in Australian clinical practice it is uncommon for the number of sessions to exceed 60, with the length of these sessions generally lasting 90 minutes at 2.4 ATA.

Mild sedatives may assist in the continuation of therapy for patients who experience anxiety from claustrophobia in the treatment chamber (MSAC 2001).

Oxygen toxicity manifests as pulmonary or neurologic changes. Seizures have been estimated to occur at a rate of about 0.01 per cent but do not seem to produce residual effects (MSAC 2001).

A search of the literature was conducted for adverse events reported since the previous report (MSAC 2001). The only available data were from case series and case reports as summarised in Tables 13 and 14.

In the study by Weaver & Churchill (2001) three female patients with cardiac disease and reduced left ventricular ejection fractions (of 1,028 patients undergoing 13,658 procedures) developed pulmonary oedema associated with HBOT. Of these, two diabetic patients aged 52 and 75 years recovered and one 77 year-old patient with severe aortic stenosis died. No reasons were given for the administration of HBOT.

The authors speculated that HBOT may have contributed to pulmonary oedema by increasing left ventricular afterload, filling pressures and oxidative myocardial stress, and by decreasing left ventricular compliance.

Ohrui et al (2002) reviewed the 39-year experience (1960 to 1998) of using HBOT at the Japan Air Self-Defence Force (Table 14). Of more than 58,000 treatments, the overall incidence of adverse events was 6.3 per cent. Ear pain was the most common adverse event, occurring in 4.79 per cent of treatment episodes. Pain in the paranasal sinuses and abdomen resulted from about 0.86 per cent and 0.34 per cent of treatments, respectively.

Plafki et al (2000) reviewed treatment complications and side effects related to HBOT in

782 patients treated for various indications with a total of 11,376 sessions in a multiplace chamber (Table 13). Pain or discomfort during decompression occurred in 216 (27.6%) patients and 12 of the 782 (1.5%) required the placement of a tympanostomy tube.

**Table 13 Adverse events associated with hyperbaric oxygen therapy: case series**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Study size** | **Type of adverse event** | **Number of events** | **Average rate per 100 sessions** | **Rate of all events per 100 sessions** | **Total number of events** |
| Ohrui,  2002 | Sessions:  58,454 | Ear pain  Paranasal sinus pain Abdominal pain Hypoxia Hyperventilation  Joint pain  Toothache  Othera | NR NR NR NR NR NR NR  NR | 4.79  0.86  0.34  0.08  0.08  0.05  0.03  0.11 | 6.29 | NR |
| Plafki,  2000 | Patients:  782  Sessions:  11,376 | Pain and/or discomfort during decompression  Tympanostomy tube placement | 216  12 | NR  NR | NR | 228 |

Abbreviations: NR, not reported

a Not specified

**HBO in cancer growth and progression**

Numerous pre-clinical studies have examined the role of HBO in initiating or enhancing the neoplastic process Feldmeier (2001). Hyperbaric oxygen directly inhibits the growth of tumour cells in culture (Kalns et al 1998) and reduces their metastatic potential (Feldmeier et al 1997). Immune suppression has not been demonstrated consistently as a mechanism of neoplastic development (Xu et al 1997, Brenner et al 1999), nor has increased cell damage due to free radical generation with HBO been established (Zamboni et al 1989, Kaelin et al 1990, Monstrey et al 1997).

The oxygen tensions used were much higher in most of these pre-clinical studies than those used clinically. In addition, the intermittent exposure to HBO seen in clinical settings is thought to induce adaptive mechanisms that reduce the damaging effects of free radicals between HBOT sessions (Feldmeier 2001).

The use of HBO to enhance the effect of radiation therapy (ie as a radiosensitiser) was first described by Johnson & Lauchlan (1966). A systematic review of 15 clinical studies on the potential effect of HBO on cancer development conducted in 1994 (Feldmeier et al 1994) and updated in 2001 (Feldmeier 2001) showed that 12 of the 15 were actually designed to test the efficacy of HBO as a radiosensitiser rather than its effect on primary neoplastic growth, cancer recurrence or metastasis (Table 14).

**Table 14 Clinical studies of exposure to HBO and cancer developmenta**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **First author, year** | **Number of patients** | **Location of cancer** | **Exposure to HBOT (Sessions x ATA)** | **Effect on cancer** |
| Johnson, 1966 | 25 | Cervix | 30 x 3 | Increased growth |
| Van Den Brenk,1967 | 85 | Head and neck | 2-6 x 3 | Decreased growth |
| Cade, 1967 | 49 | Lung and bladder | 40 x 3 | Mixed results, trending to increased growth |
| Johnson, 1974 | 64 | Cervix | 25-30 x 3 | Mixed results, trending to decreased growth |
| Henk, 1977 | 276 | Head and neck | 10 x 3 | Mixed results, trending to decreased growth |
| Henk, 1977 | 104 | Head and neck | 10 x 3 | Decreased growth |
| Bennett, 1977 | 213 | Cervix | 10 x 3 | None |
| Perrins, 1978 | 236 | Bladder | 6-40 x 3 | None |
| Watson, 1978 | 320 | Cervix | 6-27 x 3 | None |
| Dische, 1978 | 1,500 | Head and neck, bladder, lung, cervix | 6-12 x 3 | None |
| Brady, 1981 | 65 | Cervix | 10 x 3 | Decreased growth |
| Eltorai, 1987 | 3 | Urothelium | 10-20 x 2 | Increased growth |
| Denham, 1987 | 201 | Head and neck | NR | Decreased growth |
| Bradfield, 1996 | 4 | Head and neck | NR | Increased growth |
| Marx, 1999 | 405 | Head and neck | NR | Decreased growth |

Abbreviations: NR, not reported

a Adapted from Feldmeier (2001). Bibliographic details of studies cited in this table appear in Appendix G

Studies showing increased growth or tumour progression were designed without control groups. Comparative studies generally showed a lack of effect or decreased growth. The weight of clinical evidence suggests that HBO does not increase the risk of primary cancer, metastatic growth or recurrence. Feldmeier (2001) suggested that treatment should not be withheld due to concerns regarding a higher likelihood of tumour recurrence in patients where HBOT is likely to be beneficial.

In summary, estimates of the incidence of adverse events relating to HBOT collected through national registries suggested that most adverse events were self-limited and resolved after termination of therapy. As was found in the previous report on HBOT (MSAC 2001), the most common adverse events were myopia, barotrauma, claustrophobia and oxygen toxicity. Serious, life-threatening events and fatalities were rare.

## Is it effective?

**Non-healing, refractory wounds in non-diabetic patients**

Two comparative studies met the inclusion criteria, the RCT by Hammarlund & Sundberg (1994) which was previously reported under the indication of non-diabetic wounds (MSAC 2001) and a comparative study by Reedy et al (1994).

In addition, three case series met the inclusion criteria (Rosenthal & Schurman 1971, Sakakibara et al 1987, Lee et al 1989). All described the use of HBOT in the setting of wound management in the 1980s and included a number of types of non-healing wounds. The three used different interpretations of 'wound healing' as an end-point but did not describe how the outcomes were assessed, whether assessment was made using objective, valid, and consistent criteria, or whether blinding was performed. Moreover, the authors failed to report whether disease severity was comparable across patient groups. The three case series are described in detail in Appendix F1.

**Results from the randomised controlled trial**

Hammarlund & Sundberg (1994) conducted an RCT (Level II evidence) in Sweden. They recruited 16 patients (nine males) with a median age of 67 years and a range of 42 to 75 years. Patients were enrolled if: i) they had had leg ulcers for more than one year which did not appear on inspection to progress towards healing during the two months before the study, ii) ankle and first digit blood pressures were within normal ranges and iii) if

they did not smoke or suffer from concomitant chronic disease conditions such as diabetes mellitus. The authors did not report the nature or duration of any therapies prior to the administration of HBOT.

**Validity**

The study failed to meet three of the five criteria used to gauge validity. The authors did not report the method of randomisation, allocation concealment or blinding. All randomised patients were included in the analyses of outcomes at six weeks of follow-up.

**Summary of findings**

Two balanced groups of eight subjects were exposed to oxygen in a multiplace chamber at 2.5 ATA for 90 minutes, five times a week for a total of 30 sessions. The intervention group was given 100 per cent oxygen while the comparison group received air. The total length of follow-up was six weeks. Wound area was assessed as the primary outcome by placing a transparent film over the affected area, tracing the outline of the wound, scanning the film into a computer and calculating the size using a program designed specifically for the study.

The study looked at the mean changes in wound area over the course of therapy (Table

15). At four and six weeks, there were statistically significant decreases in the wound areas of those receiving 100 per cent oxygen compared to those receiving air.

**Table 15 Percentage decrease in wound area following six weeks of exposure to 100 per cent oxygen or air in a pressurised chamber**

|  |  |  |  |
| --- | --- | --- | --- |
| **Weeks of therapy** | **Percentage decrease in wound areaa**  **Mean (SD)** | | **p-valueb** |
| **100% Oxygen** | **Air** |
| 2 | 6.6 (14) | 2.8 (11) | 0.5557 |
| 4 | 22.0 (13) | 3.7 (11) | 0.0088 |
| 6 | 35.7 (17) | 2.7 (11) | 0.0004 |

Source: Hammerland & Sundberg 1994. Abbreviations: SD, standard deviation

a Compared to baseline (Week 0)

b Inter-group comparison

The authors found that improvement continued after the completion of HBOT,

although this occurred only for smaller wounds and was based on a much smaller sample size due to losses to follow up. At week 18, healing occurred in two patients who had been exposed to 100 per cent oxygen for six weeks and in no patients who received air (ITT analysis: risk difference=25%; 95% confidence interval: -5%, 55%; p=0.4667).

**Results from the non-randomised comparative study**

The observational study by Reedy et al (1994) enrolled women who had experienced wound breakdown following radical vulvectomy. The age of the study subjects ranged from 13 to 98 years. The study used historical controls (Level III-3 evidence). Eight patients who were administered HBOT following surgery for squamous or Bartholin gland carcinoma (with or without lymph node dissection, LND) in a hospital in Texas, USA were enrolled prospectively from October 1990 to March 1993. Controls (n=22) were women with or without wound breakdown selected from medical records who had undergone surgery for the same indications but were not given HBOT.

Of the eight women who underwent HBOT, relevant co-morbidities included coronary artery disease (n=2), peripheral vascular disease (n=1), congestive heart failure (n=1), malnutrition (n=1), obesity (n=1), and illegal drug use (n=1). Information on co- morbidities was not available for the comparison group.

**Validity**

Three outcomes were reported: length of hospitalisation, wound breakdown defined as separation of the wound along the incision, and infection. The authors failed to report whether outcomes were assessed objectively using specific criteria, whether assessment was performed in a blinded manner or whether follow-up was of a sufficient duration to observe relevant end-points. There were no losses to follow-up in the group receiving HBOT.

The use of historical controls in this study may have introduced specific biases relating to the selection of a comparable set of patients, since different entry criteria were used. Clearly, there is no expectation that the distribution of specific confounders would be similar between groups, but the rigour of the study would have been increased by an attempt to control for these confounding factors. As comparisons were made using historical controls any temporal improvements in wound care practices or related technologies may bias the results in favour of those receiving HBOT.

**Summary of findings**

The intervention group was initially given pre-operative antibiotic prophylaxis and pneumatic compression stockings. Closed suction drains were placed at the discretion of the surgeon. Prophylactic intravenous antibiotics were given in the first three post- operative days, after which oral antibiotics were prescribed until all drains were removed.

Patients began treatment with HBOT immediately following surgery. Pure oxygen was administered at two ATA for 90 minutes, twice a day for the first five days. If hospitalisation was required beyond five days, HBOT was continued at two ATA for 120 minutes once a day until the ninth post-operative day.

Length of hospitalisation was shorter for those patients receiving HBOT where wound breakdown did not take place (Table 16). One (16.7%) of the six patients in the intervention group who underwent LND experienced both wound breakdown and infection. Of the nine patients who underwent LND and did not receive HBOT, there were seven (77.8%) cases of wound breakdown and four (44.4%) cases of infection.

**Table 16 Wound breakdown and length of hospitalisation in patients undergoing HBOT**

**following radical vulvectomy with or without lymph node dissection**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Surgery and intervention** | **Sample size**  **(n)** | **Wound breakdown** | | **Infection** | | **Length of hospitalisation, mean (range)** |
| **n (%)** | **p-valuea** | **n (%)** | **p-valuea** |
| Vulvectomy with LND:  . Without HBOT  . With HBOT | 9  6 | 7 (77.7)  1 (16.7) | 0.041 | 4 (44.4)  1 (16.7) | 0.580 | 13.6 (7-18) with wound breakdown  6.5 (5-8) without wound breakdown  9.0 (6-15) with wound breakdown |
| Vulvectomy without  LND:  . Without HBOT  . With HBOT | 13  2 | 3 (23.1)  0 (00.0) | 1.000 | 1 (7.7)  0 (0.0) | 1.000 | 12.7 (2-21) with wound breakdown  6.8 (3-12) without wound breakdown  7.5 (6-9) with wound breakdown |

Source: Reedy et al 1994. Abbreviations: LND, lymph node dissection

a Calculated from data provided in the published article

**Refractory soft tissue radiation injuries**

One systematic review (Feldmeier & Hampson 2002) and six comparative studies (Marx et al 1985, Marx 1994, Neovius et al 1997, Carl et al 2001, Pritchard et al 2001, Hulshof et al 2002) met the inclusion criteria.

Nine case series met the inclusion criteria. Seven dealt with soft tissue radionecrosis (Roden et al 1990, Feldmeier et al 1993, Feldmeier et al 1995, Feldmeier et al 1996, Feldmeier et al 2000, Filntisis et al 2000, Yu et al 2002) and two considered other radiation injuries (Woo et al 1997, Mayer et al 2001). All shared the same methodological shortcomings identified in the previous indication, including the absence of objective and patient-relevant outcomes and blinding. The nine case studies are described in Appendix F2.

**Results from the systematic review**

A systematic review by Feldmeier & Hampson (2002) examined the evidence supporting

HBOT in the prevention or treatment of delayed radiation injury.

**Validity**

Overall the validity of the above systematic review is uncertain as the methodology of the review was inadequately described. For example the authors did not identify a discrete research question, no inclusion/exclusion criteria was specified and no search strategy was described. Therefore it is difficult to ascertain whether the primary studies included

in the systematic review were a complete and comprehensive set of studies on which to base inferential statements.

The authors appraised the quality of the supporting evidence using a number of 'review schemes'. However, neither the application of these criteria nor the reliability of decisions reached by the authors during the course of the appraisal was described. The authors' description of the review as systematic was not supported by current criteria used to assess systematic reviews.

**Summary of findings**

When considering the supporting evidence across various indications the authors applied the same decisions regardless of the weight of that evidence (Table 17). For instance, it is debatable whether the decision made by the authors that HBOT for radiation cystitis was "acceptable and useful based on very good evidence" is accurate given the evidence underlying this statement is all Level IV (one case report and 16 case series).

**Table 17 Assessment of the supporting evidence for the use of HBOT in the management of refractory soft tissue radiation injuries**

|  |  |  |  |
| --- | --- | --- | --- |
| **Indication** | **Evidence** | **Decision reached by the authorsa** | |
| **AHA scheme** | **Clinical evidence schemeb** |
| Soft tissue radio- necrosis of the head and neck | 5 case series, 1 comparative study with historical controls, 1 comparative study | Acceptable and useful based on fair to good evidence | Likely to be beneficial |
| Radiation cystitis | 1 case report, 16 case series | Acceptable and useful based on very good evidence | Likely to be beneficial |
| Radiation injuries to the chest wall and breast | 1 case report, 3 case series | Acceptable and useful based on fair to good evidence | Likely to be beneficial |
| Radiation proctitis and enteritis | 2 animal studies, 2 case reports, 10 case series | Acceptable and useful based on fair to good evidence | Likely to be beneficial |
| Miscellaneous abdominal wall and pelvic injuries | 1 case report, 2 case series | Acceptable and useful based on fair to good evidence | Likely to be beneficial |
| Various neurologic injuries | 1 animal study, 4 case reports,  7 case series, 1 RCT | From not acceptable to indeterminate to acceptable and useful based on fair to good evidence | From unlikely to be beneficial to unknown effectiveness to likely to be beneficial |
| Radiation injuries to the extremities | 1 case report, 1 case series | Acceptable and useful based on fair to good evidence | Likely to be beneficial |

Abbreviations: AHA, American Heart Association; RCT, randomised controlled trial

a Feldmeier & Hampson 2002

b Based on the Clinical Evidence (BMJ publication) scheme

In some instances, a vote-counting method was applied to derive the likelihood of benefit. In its simplest form, the vote-counting method details the number of studies showing a particular benefit compared with the number of studies showing harm. A decision is based on whether a greater number of studies show harm or benefit. The outcome of this technique does not indicate the magnitude of the effect. Moreover, a major flaw in the vote-counting process is that the quality of the studies is not considered.

In spite of these methodological problems, the references provided by Feldmeier & Hampson (2002) were evaluated for inclusion, and assessed for validity in accordance with the approach to assessment described above. No new primary studies were identified as a result of this evaluation.

**Results from randomised controlled trials**

Four RCTs (Marx et al 1985, Marx 1994, Pritchard et al 2001, Hulshof et al 2002) on the use of HBOT on a variety of indications were identified (Table 18). They examined the use of HBOT in cognitive disorders following irradiation of the brain (Hulshof et al

2002), radiation-induced plexopathy (Pritchard 2001), and healing of myocutaneous flaps following radiation (Mark 1994). The study by Marx et al (1985), previously considered

by MSAC for the prevention of osteoradionecrosis (MSAC 2001) was also considered here because it reported wound healing results.

None of the studies reported dates of enrolment. Only Pritchard et al (2001) reported the age distribution of the study population (Table 18).

**Table 18 Descriptive characteristics of randomised controlled trials of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Study location** | **Enrolment dates** | **Patient characteristics** | | | **Indication** |
| **Number of patients** | **Number of males** | **Median age**  **(years)** |
| Hulshof,  2002 | The  Netherlands | NR | 7 | NR | NR | Cognitive disorders following irradiation of the brain |
| Marx,  1994 | USA | NR | 160 | NR | NR | Healing of soft tissue flaps following radiation |
| Marx,  1985 | USA | NR | 74  (291 teeth) | NR | NR | Wound healing after tooth removal in patients at high risk of developing osteoradionecrosis |
| Pritchard,  2001 | UK | NR | 34 | 0 | 55 | Radiation-induced brachial plexopathy |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Validity**

The methodological domains related to validity in RCTs were poorly described for the four trials (Table 19). None described methods of randomisation or processes of concealment. Only the study by Pritchard et al (2001) reported blinding during outcome assessment. The same study reported two withdrawals in those receiving HBOT and near-complete follow-up at 12 months.

**Table 19 Methodological quality of randomised controlled trials of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **First author, year** | **Method of randomisation** | **Concealment of allocation** | **Inclusion of randomised participants** | **Blinding** | **Losses to follow-up** |
| Hulshof, 2002 | NR | NR | Yes | NR | None |
| Marx, 1994 | NR | NR | NR | NR | NR |
| Marx, 1985 | NR | NR | NR | NR | None |
| Pritchard, 2001 | NR | NR | 2 withdrawals | Yes | 1/72 missed assessment |

Abbreviations: NR, not reported (ie unclear, not stated, or unknown)

**Summary of findings**

**Cognitive disorders following irradiation of the brain**

Hulshof et al (2002) described a small study examining the effect of HBOT on cognitive functioning in patients with cognitive disorders after irradiation of the brain. Patients were enrolled if they: i) suffered from short-term memory loss; ii) had concentration problems or diminished speed of processing; iii) were at least 18 months post-radiation; iv) had an initial radiation dose of at least 30 Grays in three weeks (or biological equivalent); v) had no signs of tumour recurrence on computed tomography or magnetic resonance imaging; vi) were aged between 18 and 60 years; and vii) had a Karnofsky performance score of at least 70. Patients were excluded if they had concurrent severe

neurological or vascular disease, uncontrollable epileptic seizures, previous chemotherapy or a general impediment to HBOT.

Seven patients (one male) aged between 39 and 56 years were randomised to immediate treatment with HBOT or treatment with HBOT after a three-month delay. This allowed assessment of the effect of HBOT versus no therapy during the first three months while ensuring that all patients received HBOT. Pure oxygen was given over 30 HBOP sessions, administered five to six times per week, at a pressure of three ATA for 125 minutes. A battery of neuropsychological tests was administered to all patients (Table

20).

**Table 20 Neuropsychological tests used in Hulshof et al (2002)**

|  |  |
| --- | --- |
| **Test** | **Type of measurement** |
| Symbol Digit Modalities Test of the WAIS | Speed of information processing |
| Similarities of the WAIS | Ability to reason abstractly |
| Block design of the WAIS | Visual-spatial insight and visuo-constructive skills |
| Boston Naming Test | Naming line drawings of objects and animals |
| Auditory Verbal Learning Test | Verbal memory |
| Letter Fluency of the Multilingual Aphasia Examination | General vocabulary memory |
| Category Fluency of the GIT | Vocabulary memory related to animals and occupation |
| Logical Memory of the Rivermead Behavioural Memory  Test | Memory for structured verbal material |
| Calculation of the GIT | Numerical ability |
| Warrington Recognition Memory Test Faces | Aspects of non-verbal memory |
| Trailmaking Test | Executive functioning, motor speed, attention |
| Stroop Color-Word Test | Selective attention, perceptual interference, response inhibition |
| Nelson’s Modified Wisconsin Card Sorting Test | Cognitive flexibility |
| FEPSY | Reaction time and choice reaction time |
| Grooved Pegboard | Visual-motor and speed coordination |

Abbreviations: GIT, Groninger Intelligence Test; WAIS, Wechsler Adult Intelligence Scale

One patient was reported to have experienced a 'meaningful improvement' in neuropsychological functioning. After three months of follow-up, patients given HBOT reportedly experienced a 'small but not significant benefit' in neuropsychological function. Overall, six of seven patients experienced an improvement in one to nine of the 31 tests, although these did not reach statistical significance. The clinical significance of these results is unclear.

**Healing of soft tissue flaps following radiation**

The study by Marx (1994) was previously evaluated under the indication of skin graft survival (MSAC 2001). The author enrolled 160 patients requiring tissue flaps in tissues radiated to a dose greater than 6,400 centiGrays. Patients were randomly allocated to receive HBOT for 20 sessions before surgery, then 10 sessions in the post-operative period. Pressure, frequency, and duration of HBOT were not described. The therapies provided to the comparison group were not stated.

Three clinical outcomes were examined: wound infection, dehiscence and delayed wound healing (Table 21). For wound infection and dehiscence, minor and major states were differentiated but not quantified in an objective or reliable manner. Patients receiving HBOT were less likely to develop major wound infections or major wound dehiscence. Delayed wound healing was seen in 55 per cent of those who did not receive HBOT versus 11.25 per cent in those receiving HBOT.

**Table 21 Proportion of wound infection, dehiscence and delayed wound healing in patients receiving HBOT versus other therapy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Intervention group (n=80)**  **n (%)** | **Comparison group (n=80)**  **n (%)** | **p-value** |
| Wound infection:  . Minor  . Major  . Total | 3 (3.75)  2 (2.50)  5 (6.25) | 6 (7.50)  13 (16.25)  19 (23.75) | 0.3033  0.0028  0.0019 |
| Wound dehiscence:  . Minor  . Major  . Total | 6 (7.50)  3 (3.75)  9 (11.25) | 12 (15.00)  26 (32.50)  38 (47.50) | 0.1333  <0.0001  <0.0001 |
| Delayed wound healing | 9 (11.25) | 44 (55.00) | <0.0001 |

Source: Marx 1994

**Wound healing following tooth removal in patients at high risk of development of osteoradionecrosis**

Marx et al (1985) enrolled 74 patients who had an indication for removal of one or more teeth in a segment of the mandible which had received a documented absorbed dose of

6,000 rads or greater, and who agreed to maintain follow-up visits for a minimum of six months. The authors excluded patients if they had: i) received irradiation for less than six months or more than 15 years before enrolment; ii) known contraindications to penicillin or exposure to 100 per cent oxygen at 2.4 ATA; iii) showed evidence of persistent

tumour or new primary malignant disease; iv) received chemotherapy including steroid drugs within six months of enrolment; or v) concomitant systemic disease which could be expected to affect wound healing.

Patients were randomly assigned to one of two groups. The comparison group (n=37) received one million units of aqueous penicillin G intravenously before surgery and 500 mg of phenoxymethylpenicillin four times a day for 10 days after surgery. The intervention group was exposed to HBO at 2.4 ATA for 90 minutes once daily for five to six days per week. This group underwent 20 sessions before surgery, then 10 sessions

after tooth removal. As reported previously (MSAC 2001), the primary outcome reported by this study was clinical diagnosis of osteoradionecrosis during follow-up. However, only the results for wound healing were considered in the present report.

Penicillin was administered to 37 patients with 137 socket wounds. Six months after completion of therapy, 11 patients (29.7%) who were given penicillin had 31 socket wounds (22.6%) that failed to heal. In the group receiving HBOT, two patients (5.4%) had four socket wounds (2.6%) that failed to heal (Table 22).

**Table 22 Proportions of patients and tooth sockets failing to heal after six months following treatment with HBOT or penicillin**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable/Outcome** | **Intervention group** | **Comparison group** | **p-value** |
| Number of patients | 37 | 37 | na |
| Patients with unhealed tooth sockets, n (%) | 2 (5.4) | 11 (29.7) | 0.012 |
| Number of tooth sockets | 156 | 137 | na |
| Proportion of unhealed tooth sockets, n (%) | 4 (2.6) | 31 (22.6) | 0.005 |

Source: Marx et al 1985. Abbreviations: na, not applicable

**Radiation-induced brachial plexopathy**

Pritchard et al (2001) enrolled 34 patients with confirmed radiation-induced brachial plexopathy following radiation therapy for early stage breast cancer who were free from cancer recurrence and who were physically and psychologically fit for HBOT. Patients were randomly allocated to HBOT at 2.4 ATA using either 100 per cent oxygen or air comparable to 100 per cent oxygen at surface pressure (59 per cent nitrogen and 41 per cent oxygen). All participants were treated for 100 minutes including two five-minute air breaks, five days per week for six weeks to give a total of 30 sessions.

The primary end-point was the warm sensory threshold which is a measure of the function of the small sensory fibres. The test was performed with the hand resting on a paddle heated to 30°C. Participants were asked to indicate the sensation of increased temperature as it was raised by 1°C per second. As secondary end-points, the authors assessed heat pain threshold, cool sensation threshold, sensory action potentials in the median and ulnar nerves, pain using the McGill Pain Questionnaire and quality of life using the SF-36.

Two patients receiving HBOT withdrew from the study after 15 and 18 sessions, respectively.

The authors reported that there were no statistically significant differences between those receiving HBOT or air in terms of the primary or secondary sensory outcomes (Table

23).

**Table 23 Sensory outcomes following 30 sessions of HBOT versus air in patients with radiation-induced brachial plexopathy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome, follow-up** | **Change in outcome**  **Mean (SD)** | | **p-valuea** |
| **HBOT** | **Air** |
| Warm sensory threshold, °C above 30°  1 week post treatment  12 months post treatment  24 months post treatment | -0.12 (5.01)  1.41 (5.54)  1.44 (6.21) | 1.00 (3.92)  0.53 (3.43)  2.96 (5.84) | 0.4732  0.5900  0.5964 |
| Cool sensory threshold, °C  1 week post treatment  12 months post treatment  24 months post treatment | -0.24 (3.05)  2.45 (5.45)  3.45 (6.91) | 1.14 (5.23)  0.82 (5.09)  1.05 (7.18) | 0.3544  0.3822  0.4721 |
| Heat pain sensory threshold, °C  1 week post treatment  12 months post treatment  24 months post treatment | -1.76 (4.91)  1.78 (13.30)  1.66 (12.55) | 1.28 (3.76)  5.13 (12.20)  -5.59 (15.28) | 0.0511  0.4574  0.2719 |
| Sensory action potentials, median nerve, µV  1 week post treatment  12 months post treatment | 0.02 (1.63)  -0.67 (3.77) | 0.11 (0.67)  -1.03 (2.35) | 0.8346  0.7461 |
| Sensory action potentials, ulnar nerve, µV  1 week post treatment  12 months post treatment | -0.78 (1.40)  -0.69 (2.46) | -0.38 (1.17)  -1.20 (2.22) | 0.3728  0.5373 |

Source: Pritchard et al 2001. Abbreviations: SD, standard deviation

a Inter-group comparison

Although the authors reported that the results of the SF-36 showed between-group differences in emotional role function and physical function at 12 months (Table 24), they also noted that the differences were difficult to interpret and did not reflect obvious improvements in the condition. No results for the McGill Pain Questionnaire were presented.

**Table 24 Outcomes from the SF-36 following 30 sessions of HBOT versus air in patients with radiation-induced brachial plexopathy**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **SF-36 Scale** | **1 Week post treatment**  **Mean (SE)** | | **12 Months post treatment**  **Mean (SE)** | |
| **Control** | **HBOT** | **Control** | **HBOT** |
| General health | 68.4 (5.3) | 68.6 (4.9) | 61.1 (6.2) | 58.8 (5.8) |
| Mental health | 82.0 (4.0) | 73.9 (6.7) | 77.8 (3.4) | 76.5 (4.1) |
| Role-emotional | 79.2 (10.0) | 77.0 (9.4) | 66.7 (11.0) | 82.2 (7.7) |
| Social functioning | 94.3 (6.1) | 86.5 (7.2) | 93.3 (7.1) | 88.6 (6.7) |
| Vitality | 53.6 (5.4) | 47.6 (4.1) | 43.8 (3.9) | 38.7 (3.8) |
| Bodily pain | 60.4 (5.8) | 46.8 (5.8) | 54.2 (5.7) | 40.8 (4.6) |
| Role-physical | 44.2 (10.4) | 48.4 (10.5) | 29.7 (9.5) | 35.3 (10.9) |
| Physical functioning | 62.1 (5.2) | 55.4 (5.1) | 57.5 (5.4) | 53.5 (5.7) |

Source: Pritchard et al 2001. Abbreviations: SE, standard error

**Results from non-randomised comparative studies**

Two non-randomised studies compared the effectiveness of HBOT versus no treatment with HBOT in patients who had received post-operative radiation for cancers of the pharyngeal and laryngeal areas (Neovius et al 1997) or the breast (Carl et al 2001). Table

25 summarises the descriptive characteristics of these studies.

**Table 25 Descriptive characteristics of non-randomised comparative studies of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Study**  **Location** | **Study design** | **Dates of enrolment** | **Patient Characteristics** | | | **Indication** |
| **Sample size** | **Number of males** | **Mean age**  **(years)** |
| Carl,  2001 | Germany | Prospective comparative study with concurrent controls (Level III-2) | Jul 1996- Mar 1999 | 44 | 0 | NR | Late radiation injuries following breast-conserving therapy |
| Neovius,  1997 | Sweden | Retrospective, comparative study using historical controls (Level III-3) | Oct 1993- Aug 1995 | 30 | NR | 63 | Non-healing wounds following radiotherapy and surgery for oral, pharyngeal, and laryngeal cancers |

Abbreviation: NR, not reported (ie unclear, not stated or unknown)

Carl et al (2001) conducted a prospective comparative study with concurrent controls (Level III-2 evidence) that examined the effectiveness of HBOT in women with late radiation injuries following breast-conserving therapy (limited surgery and radiation therapy). Late radiation sequelae were assessed using modified LENT-SOMA criteria developed by Pavy et al (1995). Patients with symptomatic breast oedema and subjective pain greater than Grade III (persistent and intense) or with a total score of at least eight points according to the LENT-SOMA criteria were eligible for inclusion in the study.

Of 635 patients undergoing breast-conserving therapy from July 1996 to March 1999 at the Radiation Oncology Clinic of the University of Dusseldorf, 44 patients met the inclusion criteria. Of these, 32 were enrolled in the treatment group. Twelve patients refused HBOT and served as the control group. No demographic details were provided for either the treatment or control groups. The authors reported that pre-treatment scores were the same between the groups.

Neovius et al (1997) reviewed the records of 30 patients with oral, pharyngeal or laryngeal cancer classified as T2 to T4 and treated previously with radiotherapy to a dose of 52 to 62 Grays. All had major infected wounds or chronic fistulas with no sign of healing at a minimum of three weeks post surgery.

The group receiving HBOT (n=15) had been treated between October 1993 and August

1995 in a Swedish hospital. There were 10 males and the mean age of all patients receiving HBOT was 63 years. An historical comparison group (Level III-3 evidence) of a similar mean age was enrolled from an earlier period in which HBOT was not administered. As discussed previously the use of historical controls may bias the results in favour of HBOT in the event that improvements in wound care practices or related technologies arise from one assessment period to the next.

**Validity**

The major outcomes reported by Carl et al (2001) were pre- and post-treatment scores using modified LENT-SOMA criteria for subjective pain, oedema, fibrosis, telangiectasia, and erythema, as well as the sum of all scores. The validity and reliability of these criteria have been established in other studies (Hoeller et al 2003). The authors did not report blinding of outcome assessors to treatment group allocation, which may have resulted in results biased in favour of HBOT (Table 26). The authors acknowledge that there may

be systematic differences in selection or symptom grading due to the lack of randomisation that may also have resulted in bias.

The major outcome reported by Neovius et al (1997) was the healing status of the

wound, although criteria for evaluation of this end-point were not defined. It was unclear whether outcomes were assessed objectively using specific criteria, whether assessment was performed in a blinded manner or whether follow-up was of sufficient duration to observe relevant end-points (Table 26).

Similar to Reedy et al (1994), the use of historical controls by Neovius et al (1997) may have introduced specific biases relating to the selection of a comparable set of patients since entry criteria were not explicitly reported. Additionally, no attempt was made to adjust for known confounders. Temporal progress of improvements in wound care or technology, especially as it relates to comparisons between different time periods, may bias the results in favour of HBOT.

**Table 26 Validity characteristics of non-randomised comparative studies of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **First author, year** | **Comparable groups at inception** | **Identification and adjustment for confounding factors** | **Blind outcome assessment** | **Sufficient duration of follow-up** | **Proportion lost to follow-up** |
| Carl, 2001 | NR | No | NR | NR | None |
| Neovius, 1997 | NR | No | NR | NR | None |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Summary of findings**

**Late-radiation sequelae following breast-conserving therapy**

Patients undergoing HBOT received treatment at a pressure of 240 kPa (2.4 ATA) for a breathing time of 90 minutes and a median total number of 25 sessions (range 7 to 60) at a rate of five times per week (Carl et al 2001). Patients continued therapy until three consecutive treatments failed to show any further improvement in the outcome scores.

Results are presented in Table 27. Carl et al (2001) reported statistically significant improvements in post-treatment scores for pain, oedema, erythema and the total score in patients treated with HBOT compared to those not receiving HBOT. No statistically significant differences in scores were observed between the treatment groups for fibrosis and telangiectasia.

**Table 27 Outcomes in patients receiving HBOT versus no HBOT (Carl et al 2001)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **HBOTa (n=32) Median (range)** | **No HBOTb (n=12) Median (range)** | **p-value** |
| Pain Score Pre-treatment Post-treatment | 3 (1-4)  0 (0-2) | 3 (1-3)  3 (1-4) | <0.001 |
| Oedema score Pre-treatment Post-treatment | 3 (1-3)  1 (0-2) | 2 (0-3)  2 (0-3) | <0.001 |
| Fibrosis score Pre-treatment Post-treatment | 0 (0-3)  0 (0-3) | 0 (0-3)  0 (0-3) | NS |
| Telangiectasia Pre-treatment Post-treatment | 0 (0-3)  0 (0-3) | 0 (0-2)  0 (0-2) | NS |
| Erythema  Pre-treatment  Post-treatment | 2 (0-3)  0 (0-2) | 3 (0-3)  0 (0-2) | <0.001 |
| Total score Pre-treatment Post-treatment | 9 (6-14)  2 (0-6) | 8 (3-12)  7 (3-12) | <0.001 |

Abbreviations: NS, not significant – the actual value was not reported

a Median follow-up was 11 months with a range of 1-32

b Median follow-up was 7 months with a range of 2-38

Carl et al (2001) concluded that patients experienced an improvement in clinical state during the course of hyperbaric oxygen therapy for pain, oedema and erythema.

**Non-healing wounds following radiotherapy and surgery for oral, pharyngeal, and laryngeal cancers**

Neovius et al (1997) reported that patients received antibiotics, minor surgery, and wound dressings as required. The HBOT group received 100 per cent oxygen at 2.5 to

2.8 ATA for between five and 40 treatments of 75 minutes' duration. Patients were initially scheduled to receive 30 treatments. If wounds had not healed when this stage was reached, another 10 treatments were given.

Results are presented in Table 28. There was a statistically significant increase in the probability of complete wound healing in those undergoing HBOT (p=0.045). Two patients in the comparison group suffered from severe haemorrhage post-operatively and died. There were no fatalities in the group receiving HBOT.

**Table 28 Outcomes in patients receiving HBOT versus no HBOT (Neovius et al 1997)**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **HBOT Group**  **(n=15)** | **Comparison Group**  **(n=15)** |
| Complete healing | 12 | 7 |
| Partial healing | 2 | 1 |
| Failure to heal | 1 | 7 |

**Discussion**

Although evidence in support of the effectiveness of HBOT in the treatment of non- healing wounds in non-diabetic patients and of refractory soft tissue radiation injuries included higher level evidence study designs (RCTs and non-RCTs), this evidence was deemed to be of low methodological quality because it failed to meet relevant validity criteria. Furthermore, the majority of studies reported end-points that were of uncertain clinical significance or patient relevance. Where relevant outcomes were reported, their validity was uncertain due to a lack of objective or blinded assessment and the failure to report explicit measurement criteria.

**Non-healing wounds in non-diabetic patients**

Only two controlled studies of HBOT for non-healing wounds in non-diabetic patients met the entry criteria. One RCT showed decreased wound area with HBOT while a comparative study using historical controls showed trends toward the prevention of wound breakdown and infection, as well as reductions in length of hospitalisation.

**Refractory soft tissue radiation injuries**

Six controlled studies of HBOT for refractory soft tissue radiation injuries met the inclusion criteria. Four RCTs examined four different sub-indications related to radiation therapy. A small RCT examining the use of HBOT for cognitive impairment following brain irradiation showed no significant improvement in neuropsychological function. Another RCT that evaluated HBOT for radiation-induced brachial plexopathy showed

no significant differences in sensory thresholds or quality of life between those receiving HBOT and controls. Another RCT showed that HBOT improved wound healing in patients at high risk of osteoradionecrosis. The fourth RCT showed that HBOT reduced the likelihood of major wound infection, major wound dehiscence, and delayed wound healing in myocutaneous grafts in patients who had previously undergone radiation therapy.

There is general acceptance among radiation biologists that the underlying pathogenesis of radiation injury is common to all tissues, although the latency of onset and mode of expression of radiation injury can vary widely (Denham et al 2001; Travis 2001). Clinical opinion suggests that there is no reason to postulate inherent differences between the necrosis of soft tissue and that of bone.

All studies failed to meet the criteria used to assess the quality in RCTs. For instance, it is known that effect sizes are overestimated in RCTs if particular methodological parameters such as description of the randomisation process, allocation concealment procedures, or blinding, are not met (Schulz et al 1995). This failure limited the extent to which inferences and generalisations could be made.

Two on-going clinical trials were found (Appendix E). In the area of refractory soft tissue radiation injuries, the National Centre for Complementary and Alternative Medicine (NCCAM) of the US National Institutes of Health is presently sponsoring a trial on the efficacy of HBOT in patients who have undergone laryngectomies and radiation for cancer. A larger study sponsored by the Baromedical Research Foundation is also under way. Both trials are in the stages of recruitment. Dates of completion are not presently known.

Three case series reporting on non-healing, refractory wounds in non-diabetic patients and nine dealing with refractory soft tissue radiation injuries were identified which enrolled consecutive patients. While the considerable potential for bias inherent in their design limited the use of the information contained in these case series, it was included to supplement the evidence available from the more rigorous comparative studies.

**Limitations of the review of safety and effectiveness**

While items from the grey literature (eg conference proceedings, abstracts, etc) identified by expert opinion were included, the search strategy was not designed to capture publications from these sources. However, the likelihood of missing good quality RCTs was minimised by searching trial registries and other databases including those specific to HBOT for HBO evidence.

The inclusion of Level IV studies in the form of case series expanded the breadth of evidence over that of the previous report. Moreover, since the decision to include studies was made independently of the assessment of quality, there was little chance that relevant studies would have been missed.

A large proportion of the evidence has been published as case series. Non-comparative studies are useful as initial positions against which the potential effectiveness of technologies may be viewed. However, they are of limited value in determining the effectiveness of new technologies in the complex milieu of existing therapy.

Assessment of the quality of case series evidence is challenging. There is no validated instrument and inherent biases exist in the interpretation of the comparative

effectiveness of interventions from such study designs. A modification of the NHS CRD criteria was applied to determine the quality of the Level IV evidence. The reviewers developed additional criteria that do not appear in the original CRD inventory. These criteria were chosen *a priori* based on items appearing in studies of more rigorous design, but some degree of subjectivity was necessary to attain consensus among the reviewers

on the final criteria.

A sensitive search strategy identified a wide range of studies and indications which required clinical expertise for determination of their eligibility for inclusion under the entity 'soft tissue radiation injuries' (eg cognitive impairment, plexopathy, etc). The use of such a sensitive strategy reduced the possibility that relevant studies may be missed.

# What are the economic considerations?

The earlier report (MSAC 2001) included calculation of the cost-effectiveness of HBOT for a number of indications for which some evidence suggested the treatment was effective. The likely average cost of monoplace HBOT treatment was calculated under a range of assumptions about capacity utilisation, capital cost, and staffing. The current report used those indicative costs and applied them to the evidence for the effectiveness of HBOT in refractory soft tissue radiation injuries and non-healing wounds in non- diabetic patients.

The estimated direct cost of HBOT (MSAC 2001) was not based on a prospective study of HBOT treatment in clinical practice in Australia and was therefore unable to assess fully the implications for overall disease management. Given these limitations on the cost data, the present report can only provide an indication of the potential cost-effectiveness of HBOT in Australian practice.

It was estimated that the average cost of a course of treatment (30 sessions in a monoplace unit) was $6,941 with a range of $2,466 to $9,255 depending on the number of chambers in operation (one to four) and the number of sessions (15 to 40) (MSAC

2001, Appendix E). The direct cost made allowance for a feasible number of patients in a day and included staffing, overhead, maintenance, and capital costs.

## Non-healing, refractory wounds in non-diabetic patients

As reported (MSAC 2001), Hammarlund & Sundberg (1994) exposed two groups of

eight subjects with leg ulcers of more than one year’s duration to different concentrations of oxygen in a multiplace chamber, five times a week for a total of 30 sessions.

The study looked at the mean changes in wound area over the course of therapy (Table

15). At four and six weeks of therapy, there were statistically significant decreases in the wound areas of the HBOT group compared to the comparison group. The HBOT group had a 35.7 per cent decrease in wound area from baseline at six weeks compared to 2.7 per cent decrease in wound area for the comparison group. This suggested that HBOT treatment of chronic leg ulcers might result in an expected one-third reduction in wound area for a treatment cost of $6,941 per patient.

The clinical significance of this outcome or its significance to patient welfare in the longer term is not sufficiently clear to allow assessment of whether this figure is acceptable. The study also reported an increase in healing at week 18 of 25 per cent which suggests an apparent extra $27,764 per additional person cured of a chronic leg ulcer in the study. However, given the p-value of 0.4667 for the risk difference in the study, it is not possible to be confident that this is a reasonable estimate of the cost- effectiveness of HBOT for this indication.

The comparative study by Reedy et al (1994) of HBOT in women who had experienced wound breakdown following radical vulvectomy suggested that there might be reductions in hospital stay as well as wound breakdown and post procedure infections. The

reduction in mean length of hospital stay (Table 16) was less than five days when all wounds were considered and HBOT was given for an average of nine days as ten 90- minute sessions and four two-hour sessions.

Using the cost calculations in the previous report (MSAC 2001), the direct cost of HBOT amounts to $3,430. While a reduction in length of stay would offset that direct cost, it may not lead to financial savings. No accurate data are available on the cost of an extra day in hospital for this indication in Australia. In any case, the study design and sample size in Reedy et al (1994) are such that it is not possible for reliable inferences about the use of resource and comparative health outcomes to be made.

Cianci et al (1988) examined the costs and outcomes of HBOT for patients with serious lesions of the lower extremity that had proven refractory to standard medical or surgical treatments. The patients were given one or two treatments of 1.5 to 2 hour's duration at two ATA in a monoplace chamber. The study did not explicitly report the results for the non-diabetic wounds of 20 of the 39 patients, however re-analysis of the data suggested an average cost of hospital treatment of US$25,281. There appeared to be one amputation in the non-diabetic group at a reported cost of US$26,000 to US$30,000 and a further cost of comprehensive rehabilitation in California in excess of US$40,000. On this basis, the study suggested that HBOT compared favourably with the cost of

standard treatment for those with limb-threatening refractory lesions of the leg.

In this study the cost of treatment with HBOT was 36 per cent of the expected total cost of surgery and rehabilitation for a patient requiring amputation. The study claims that there would be financial savings if HBOT resulted in at least 36 per cent fewer amputations among patients with serious lesions of the lower extremity that had proven refractory to standard medical or surgical treatments. The study did not provide evidence about the likely outcomes and treatment costs for a group of patients without HBOT. It is, therefore, not possible to conclude that there would be either reduced amputations or consequent savings as a result of HBOT.

## Refractory soft tissue radiation injuries

An evaluation by the Canadian agency Agence d’Evaluation des Technologies et des Modes d’Intervention en Santé (AETMIS 2001) drew on the findings of Marroni et al (1996) to calculate the financial savings from reduced length of hospital stay arising from HBOT in five conditions including problem wounds.

AETMIS (2001) suggested substantial savings in hospital expenditure in excess of direct HBOT costs associated with a 58 to 75 percent reduction in mean length of stay. Even if a similar reduction in length of stay could be inferred from these data, the evidence in Marroni et al (1996) was not of sufficiently quality to substantiate such a claim. The average cost of a session of HBOT at €120 is higher than the cost in Australia, but the reduction in length of stay in Marroni et al (1996) was not demonstrated convincingly. As the AETMIS study stated, Marroni et al (1996) merely gave the length of stay without explaining the protocol used to compare the two situations (with and without HBOT). Neither the study by Marroni et al (1996) nor the AETMIS review (AETMIS 2001) have demonstrated that such results would be achieved in Australia for HBOT compared to standard treatment for problem wounds including leg ulcers or soft tissue radionecrosis.

Marx (1994), in what was described as a randomised prospective study of wound complications related to soft tissue flaps and wound healing, suggested that HBOT led to a relative reduction in wound dehiscence, reduced infection, and improved wound healing. Each of these outcomes has the potential to lead to reduced health care resource use in terms of antibiotic use, wound irrigations, debridement surgery and hospital stay.

Marx (1994) reported the use of HBOT following the application of myocutaneous grafts to subjects requiring major soft tissue surgery or flap after radiation therapy. However, since neither the intervention nor the comparison therapies were adequately described, and no details of the frequency and duration of HBOT exposure were given, it was difficult to estimate the economic consequences of therapy. As stated previously (MSAC

2001), 'exposure to HBOT may well demonstrate a beneficial effect on the survival of split skin grafts and myocutaneous flaps, but the study (Marx 1994) possesses serious flaws that strictly limit its generalisability'. As a result, it is not, possible to reach a conclusion about the cost-effectiveness of HBOT in soft tissue radiation injuries.

A case study reported by Boykin et al (1997) estimated that HBOT would lead to a 31 per cent reduction in the expected cost of treatment for a radionecrotic wound. However, since this estimate is based on a single case study with a simulated untreated case, it cannot be regarded as sufficient evidence of actual costs saved from adjunctive HBOT for radiation injuries.

Only Pritchard et al (2001) included a measure of quality of life following treatment with HBOT. They reported the results of the SF-36 health status measures following 30 sessions of HBOT versus air in patients with radiation-induced brachial plexopathy. Quality of life at one week and 52 weeks appeared to have deteriorated in both groups and any differences between the groups were not consistently in favour of HBOT.

# Conclusions

## Safety

Estimates of the incidence of adverse events relating to HBOT collected through

national registries suggested that most adverse events were self-limited and resolved after termination of therapy. As reported previously (MSAC 2001), the most common forms of adverse events were myopia, barotrauma, claustrophobia and oxygen toxicity. Serious, life-threatening events and fatalities were rare.

## Effectiveness

**Non-healing wounds in non-diabetic patients**

Two controlled studies of HBOT for non-healing wounds in non-diabetic patients met entry criteria. One RCT showed a decrease in wound area while a comparative study using historical controls showed trends toward the prevention of wound breakdown and infection, and reductions in length of hospitalisation.

**Refractory soft tissue radiation injuries**

Six controlled studies of HBOT for refractory soft tissue radiation injuries met inclusion criteria. Four RCTs examined four different sub-indications related to radiation therapy. One small RCT examining the use of HBOT for cognitive impairment following brain irradiation showed non-significant improvement in neuropsychological function. Another RCT evaluating HBOT for radiation-induced brachial plexopathy showed no significant differences in sensory thresholds or quality of life between those receiving HBOT and controls. In a group of patients at high risk for the development of osteoradionecrosis, HBOT was found to increase the healing of tooth socket wounds following extraction compared to the administration of penicillin. The fourth RCT showed that HBOT reduced the likelihood of major wound infection and major wound dehiscence and delayed wound healing in myocutaneous grafts in patients who had undergone radiation therapy.

## Cost-effectiveness

Chronic refractory wounds have a high morbidity that can have severe consequences on the quality of life of patients and their families as well as resulting in high acute care and rehabilitation costs for the health care system. This is particularly the case if there is a risk of a major amputation. To the extent that a course of treatment of HBOT could reduce that morbidity at a cost of $6,941, it has the potential to be a very cost effective intervention.

The clinical evidence was inadequate to substantiate claims that HBOT was cost effective in the treatment of refractory soft tissue radiation injuries or non-diabetic refractory wounds. There was not evidence of sufficient quality to substantiate claims that it will either lead to an overall saving in resource use, or that it would lead to substantial patient relevant gains in health related quality of life compared to current medical treatments at an acceptable cost.

# Recommendations

The clinical evidence was inadequate to substantiate claims that hyperbaric oxygen therapy (HBOT) was cost-effective in the treatment of refractory soft tissue radiation injuries or non-diabetic refractory wounds. However, MSAC recommended that, as there are no effective alternative therapies and in view of the progress of local data collections and an international trial, funding for HBOT continue for MBS listed indications at currently eligible sites, for a further three years.

- The Minister for Health and Ageing accepted this recommendation on 31 August 2004.

# Appendix A - MSAC terms of reference and membership

MSAC's terms of reference are to:

• advise the Minister for Health and Ageing on the strength of evidence pertaining to new and existing medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;

• advise the Minister for Health and Ageing on which new and existing medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;

• advise the Minister for Health and Ageing on references related either to new or existing medical technologies and procedures; and

• undertake health technology assessment work referred by the Australian Health

Ministers’ Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumer issues, and health administration and planning:

|  |  |
| --- | --- |
| **Member** | **Expertise or Affiliation** |
| Dr Stephen Blamey (Chair) | general surgery |
| Professor Bruce Barraclough | general surgery |
| Professor Syd Bell | pathology |
| Dr Paul Craft | clinical epidemiology and oncology |
| Associate Professor Jane Hall | health economics |
| Dr Terri Jackson | health economics |
| Ms Rebecca James | consumer health issues |
| Professor Brendon Kearney | health administration and planning |
| Associate Professor Richard King | internal medicine |
| Dr Ray Kirk | health research |
| Dr Michael Kitchener | nuclear medicine |
| Mr Lou McCallum | consumer health issues |
| Dr Ewa Piejko | general practice |
| Professor John Simes | clinical epidemiology and clinical trials |
| Mr Chris Sheedy | Assistant Secretary, Diagnostics and Technology Branch, Australian Government Department of Health and Ageing |
| Dr Robert Stable | Australian Health Ministers’ Advisory Council representative |
| Professor Bryant Stokes | neurological surgery |
| Associate Professor Ken Thomson | radiology |
| Dr Douglas Travis | urology |

# Appendix B Supporting Committee

**Supporting committee for MSAC application 1054: Hyperbaric oxygen therapy for non-healing, refractory wounds in non-diabetic patients and refractory soft tissue radiation injury**

|  |  |
| --- | --- |
| **Professor Peter Phelan (Chair)**  BSc, MBBS, MD, FRACP, MRACMA Emeritus Professor of Paediatrics University of Melbourne | Member of MSAC |
| **Dr Michael Bennet**  MBBS, DA(Eng), FANZCA, MM(ClinEpi), DipDHM  Department of Diving and Hyperbaric Medicine  Prince of Wales Hospital, NSW | Nominated by the Australian and New Zealand Hyperbaric Medicine Group |
| **Dr Stephen Blamey**  MBBS, FACS, FRACS  Head of Gastrointestinal Surgery, Monash  Medical Centre  Chair, Infection Control Advisory Committee  Southern Health | Chair of MSAC |
| **Dr Michael Leung**  MBBS, FRACS  Head, Plastic and Reconstructive Surgery Unit  The Alfred Hospital | Co-opted member |
| **Professor Lester Peters**  MBBS(Hons), MD, FRANZCR, FACR, AM Professor of Radiation Oncology  Peter MacCallum Cancer Institute | Co-opted member |
| **Dr John M Quinn**  MBBS, FRACS, FACS  Senior Visiting Vascular Surgeon, and Senior  Visiting Transplant Surgeon  Princess Alexandra Hospital Brisbane  Senior Visiting Vascular Surgeon  Mater Miseracordiae Hospital Brisbane Examiner in Vascular Surgery RACS (Senior Examiner Elect) | Co-opted member |

**Dr David Smart**

BMedSci(Tas), MBBS(Hons), FACEM, FACTM, F DipDHM

Medical Co-Director, Department of Diving and

Medicine

Royal Hobart Hospital.

Director of Emergency Medicine

Calvary Health Care Tasmania

Senior Clinical Lecturer, Faculty of Health Science

University of Tasmania

Chair Scientific Committee

Australasian College for Emergency Medicine

Co-opted member

**Dr Ross Taylor**

MBBS, FRACP, DDU, Ct Aerospace Medicine, GrDTh

General Practitioner, Senior Examiner RACGP

Nominated by the Royal Australian College of General Practitioners

**Mrs Robin Toohey** AM Nominated by the Consumers’ Health Forum of Australia

**Dr David Wilkinson**

MBBS, DipRACOG, DA(UK), FANZCA Director, Hyperbaric Medicine Unit

Royal Adelaide Hospital

Co-opted member

**Dr Robert Wong**

BSc, MBBS, FFARACS, FANZCA, DipDHM Medical Director

Department of Diving and Hyperbaric Medicine

Fremantle Hospital

Nominated by the Australian and New Zealand College of Anaesthetists

# Appendix C Studies included in the review

**Included studies: Non-healing, refractory wounds in non- diabetic patients**

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**Included studies: Refractory soft tissue radiation injuries**

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# Appendix D Studies excluded from the review

**Non-healing, refractory wounds in non-diabetic patients**

**Pre-clinical (animal) studies**

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# Appendix E Clinical trial registries and HTA websites searched

**Ongoing clinical trials**

**Efficacy of Hyperbaric Oxygen Therapy in Laryngectomy Patients**

This study, sponsored by the National Centre for Complementary and Alternative Medicine (NCCAM), was designed to develop a predictive model for the development of wound complications in patients undergoing laryngectomy surgery for laryngeal/adjoining structure cancers, and to evaluate the clinical efficacy of hyperbaric oxygen for the prevention/management of wound complications in this previously irradiated population. Patients are enrolled if in need of laryngectomies for newly- diagnosed cancers and for failed chemoradiation.

**Baromedical Research Foundation Project HORTIS (Hyperbaric Oxygen Radiation**

**Tissue Injury Study)**

Project HORTIS was conceived to increase the current level of evidence regarding HORT and better determine its effectiveness. HORTIS will involve a total of eight different trials – seven at separate anatomic sites and one prophylactic arm. The seven sites are the mandible, larynx, skin, bladder, rectum, colon and cervix.

HORTIS was designed as a multi-centre randomised and double-blinded controlled clinical trial with patient cross-over. Recruitment has been under way since 1999. The first institution to become a part of HORTIS is the Mexican National Cancer Institute (INCAN). Additional centres that have completed their institutional ethics review process are Vancouver General Hospital, British Columbia Canada; Palmetto Richland Memorial Hospital, Columbia, South Carolina, USA; The University of Istanbul Medical Centre, Turkey; Prince of Wales Hospital, Sydney, NSW, and the Royal Adelaide Hospital, Adelaide, SA. Institutions in Israel and Europe have expressed preliminary interest.

**Clinical trial registries searched**

Current Controlled Trials

www.controlled-trials.com/ (Accessed 10 January 2003)

UK National Research Register

[www.update-software.com/National/](http://www.update-software.com/National/) (Accessed 10 January 2003)

NHMRC Clinical Trials Centre [www.ctc.usyd.edu.au/](http://www.ctc.usyd.edu.au/) (Accessed 10 January 2003)

**HTA websites searched**

Agence d’Évaluation des Technologies et des Modes d’Intervention en Santé (AETMIS)

[www.aetmis.gouv.qc.ca](http://www.aetmis.gouv.qc.ca/) (Accessed 13 January 2003)

Agencia de Evaluación de Tecnologías Sanitarias (AETS)

[www.isciii.es/aets/](http://www.isciii.es/aets/) (Accessed 13 January 2003)

Agencia Andaluza de Evaluación de Tecnologías Sanitarias (AETSA)

[www.csalud.junta-andalucia.es/orgdep/AETSA/default.htm](http://www.csalud.junta-andalucia.es/orgdep/AETSA/default.htm) (Accessed 13 January 2003)

Alberta Heritage Foundation for Medical Research (AHFMR)

[www.ahfmr.ab.ca/](http://www.ahfmr.ab.ca/) (Accessed 13 January 2003)

Agency for Healthcare Research and Quality (AHRQ)

[www.ahrq.gov/](http://www.ahrq.gov/) (Accessed 13 January 2003)

Agence Nationale d'Accréditation et d'Évaluation en Santé (ANAES) [www.anaes.fr/ANAES/anaesparametrage.nsf/HomePage?ReadForm](http://www.anaes.fr/ANAES/anaesparametrage.nsf/HomePage?ReadForm) (Accessed 13 January 2003)

Agence Nationale pour le Dévéloppement de l'Évaluation Medicale (ANDEM)

[www.upml.fr/andem/andem.htm](http://www.upml.fr/andem/andem.htm) (Accessed 13 January 2003)

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical

(ASERNIP-S)

[www.racs.edu.au/open/asernip-s.htm](http://www.racs.edu.au/open/asernip-s.htm) (Accessed 13 January 2003)

British Columbia Office of Health Technology Assessment (BCOHTA)

[www.chspr.ubc.ca/](http://www.chspr.ubc.ca/) (Accessed 13 January 2003)

Catalan Agency for Health Technology Assessment and Research (CAHTA)

[www.aatm.es/ang/ang.html](http://www.aatm.es/ang/ang.html) (Accessed 13 January 2003)

Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA)

[www.ccohta.ca/](http://www.ccohta.ca/) (Accessed 13 January 2003)

German Institute for Medical Documentation and Information (DIMDI)

[www.dimdi.de/homeeng.htm](http://www.dimdi.de/homeeng.htm) (Accessed 13 January 2003)

Danish Centre for Evaluation and Health Technology Assessment www.dihta.dk/ (Accessed 13 January 2003)

Finnish Office for Health Care Technology Assessment (FINOHTA)

[www.stakes.fi/finohta/e/](http://www.stakes.fi/finohta/e/) (Accessed 13 January 2003)

Health Council of the Netherlands (GR)

[www.gr.nl/](http://www.gr.nl/) (Accessed 13 January 2003)

Minnesota Health Technology Advisory Committee [www.health.state.mn.us/htac/](http://www.health.state.mn.us/htac/) (Accessed 13 January 2003)

Institute of Clinical Systems Improvement (ICSI)

[www.icsi.org/](http://www.icsi.org/) (Accessed 13 January 2003)

Institute of Technology Assessment of the Austrian Academy of Sciences [www.oeaw.ac.at/ita/welcome.htm](http://www.oeaw.ac.at/ita/welcome.htm) (Accessed 13 January 2003)

International Network of Agencies of Health Technology Assessment (INAHTA)

[www.inahta.org/](http://www.inahta.org/) (Accessed 13 January 2003)

Medical Technology and Practice Patterns Institute (MTPPI)

www.mtppi.org/frameset.asp?Pg=/&MI=1 (Accessed 13 January 2003)

National Co-ordinating Centre for Health Technology Assessment (NCCHTA)

[www.hta.nhsweb.nhs.uk/](http://www.hta.nhsweb.nhs.uk/) (Accessed 13 January 2003)

National Horizon Scanning Centre [www.publichealth.bham.ac.uk/horizon/](http://www.publichealth.bham.ac.uk/horizon/) (Accessed 13 January 2003)

National Institute for Clinical Excellence (NICE)

[www.nice.org.uk/](http://www.nice.org.uk/) (Accessed 13 January 2003)

New Zealand Health Technology Assessment (NZHTA)

nzhta.chmeds.ac.nz/ (Accessed 13 January 2003)

Swedish Council on Health Technology Assessment in Health Care (SBU)

www.sbu.se/admin/index.asp (Accessed 13 January 2003)

Swiss Centre for Technology Assessment (TA-SWISS)

www.ta-swiss.ch/ (Accessed 13 January 2003)

The Norwegian Centre for Health Technology Assessment www.oslo.sintef.no/smm/news/FramesetNews.htm (Accessed 13 January 2003)

TNO Prevention in Health (TNO)

[www.health.tno.nl/homepage\_pg\_en.html](http://www.health.tno.nl/homepage_pg_en.html) (Accessed 13 January 2003)

Veterans Affairs Health Services Research and Development [www.hsrd.research.va.gov/](http://www.hsrd.research.va.gov/) (Accessed 13 January 2003)

World Health Organisation Health Technology and Pharmaceuticals [www.who.int/technology/](http://www.who.int/technology/) (Accessed 13 January 2003

# Appendix F1

**Non-healing, refractory wounds in non-diabetic wounds: case series meeting primary inclusion criteria**

**Table 29 Descriptive characteristics of case series evaluating HBOT in non-healing, refractory wounds in non-diabetic patients**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Study location** | **Dates of enrolment** | **Number of patients** | **Number of males** | **Mean age**  **(years**±**SD)** | **Co-morbidities** | **Inclusion/Exclusion criteria** |
| Lee,  1989 | China | 1976 to 1987 | 149/1,288 (chronic ulcer patients only) | 99 | 41.2±36.8  Range: 6-78 | NR | All patients treated between 1976 and 1987 at the Department of Diving and Hyperbaric Medicine, Naval General Hospital, Kaoshing |
| Rosenthal,  1971 | USA | NR | 18 | 14 | Range: 15-67 | Vascular disease: 2  Quadriplegia: 3  Paraplegia: 12  Fracture: 1 | All patients presenting with pressure ulcers treated at the authors' facility at the time of publications |
| Sakakabira,  1987 | Japan | 1966 to 1983 | 149/161 (non-diabetics) | NR | NR | Burger’s disease  Obstructive arteriosclerosis | Although no inclusion/exclusion criteria was reported all patients had received surgical treatment for chronic peripheral vascular disease and other adjunctive treatments that did not provide relief |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Table 30 HBOT regimens used in case series of non-healing, refractory wounds in non-diabetic patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Type and location of wound** | **Time from wound/lesion to HBOT** | **Therapies tried before HBOT** | **Duration of therapy tried before HBOT** | **HBOT regimen** | **Concomitant therapies** |
| Lee,  1989 | Chronic ulcers | NR | NR | NR | Oxygen pressure and treatment schedules not reported  Mean number of treatments:  25.2±36.8; Range: 3-280 | NR |
| Rosenthal,  1971 | Pressure sores | NR | Standard ulcer treatment including mechanical cleansing, frequent dressing changes, mechanical debridement and Hubbard tank therapy | NR | 3 ATA for 1.2 hours daily, 5 days per week  Mean number of treatments: 37  Range: 14-60 | Standard ulcer treatment including mechanical cleansing, frequent dressing changes, mechanical  debridement and Hubbard tank therapy |
| Sakakabira,  1987 | Chronic peripheral vascular disease (location of ulcers not reported) | NR | Arteriography or artography Sympathectomy or arterial reconstructive surgery | NR | 2 ATA for 75 minutes once a day for a total of 30 to 50 sessions | Most patients received cytochrome C |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Table 31 Validity characteristics of case series examining HBOT in non-healing, refractory wounds in non-diabetic patients**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Explicit inclusion/exclusion criteria** | **Outcomes assessed in all patients** | **Uniform follow up** | **Measurement of outcomes** | **Outcomes quantified** | **Outcomes measured objectively** | **Blinded assessment of outcome** | **Indication/Disease severity uniform across patients** | **Description given of failed treatment** |
| Lee,  1989 | No | Yes | NR | NR | No | No | NR | NR | NR |
| Rosenthal,  1971 | No | Yes | NR | NR | No | No | NR | NR | Yes |
| Sakakabira,  1987 | No | Yes | NR | NR | No | No | NR | NR | Yes |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Table 32 Results of case series examining HBOT in non-healing, refractory wounds in non-diabetic patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **First author, year** | **Outcomes reported** | **Result** | **Length of follow-up** |
| Lee,  1989 | Cured  Improved  Invalid | 77/149 (51.7%)  57/149 (38.3%)  15/149 (10%) | NR |
| Rosenthala,  1971 | Improved  Required Surgery for closure  Healed | 27/38 (71%)  11/38 (29%)  22/38 (58%) | NR |
| Sakakabira,  1987 | Soreness: ASO  TAO  Ulcer: ASO TAO  Amputation Required: Fingers or Toes:  ASO TAO  Extremities: ASO  TAO | 74/106 (70%) improved  30/43 (70%) improved  35/43 (81%) improved  84/106 (79%) improved  6/43 (14%)  16/106 (15%)  4/43 (9.3%)  12/106 (11.3%) | NR |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

a The 18 patients in the study had a total of 38 wounds

# Appendix F2

**Refractory soft tissue radiation injuries: case series meeting primary inclusion criteria**

**Table 33 Descriptive characteristics of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Study location** | **Dates of enrolment** | **Number of patients** | **Number of males** | **Mean age**  **(years**±**SD)** | **Co-morbidities** | **Inclusion/Exclusion criteria** |
| Feldmeier,  1993 | USA | 1980 to 1985 | 9 | 9 | 64.8±8.3  Range: 56-82 | NR | Inclusion: All patients referred for HBO and treated for laryngeal necrosis at the hyperbaric medicine facility at Southwest Methodist Hospital, San Antonio, Texas, between 1980 and 1985 who had not had a total laryngectomy before referral |
| Feldmeier,  1995 | USA | From 1980 onwards | 8 patients with  23 soft tissue injuries | 1 | 55.25±14.37  Range: 21-87 | NR | Inclusion: Review of all patients with chest wall radiation necrosis referred to the hyperbaric medicine departments of Southwest Texas Methodist and Nix Hospitals, San Antonio, Texas |
| Feldmeier,  1996 | USA | From 1979 onwards | 42 with 44 soft tissue injuries | 8 | 62.52±12.71  Range: 33-84 | NR | Inclusion: All patients treated at Southwest Texas Methodist and Nix Hospitals, San Antonio, Texas for non-healing necrotic wounds of the extremities within previously irradiated fields between the years of 1979 to 1997 |
| Feldmeier,  2000 | USA | 1979 to 1997 | 17 | 8 | 62.68±18.5  Range: 31-87 | NR | Inclusion: All patients treated at Southwest Texas Methodist and Nix Hospitals San Antonio, Texas for non-healing necrotic wounds of the extremities within previously irradiated fields between the years of 1979 to 1997 |
| Flintisis,  2000 | USA | 1990 to 1996 | 18 | 11 | 59.61±10.03  Range: 41-77 | Hyponatremia (1) Chronic renal failure (3) Hypertension (3)  COPD (3)  Lung carcinoma (1) Diabetes (3)  Angina (1)  Basal cell carcinoma of the skin (1) Rheumatoid arthritis (1)  Alcohol abuse (1) | Inclusion: All patients referred for HBO therapy to the FG Hall Hyperbaric Center at Duke University Medical Center Durham, North Carolina with the diagnosis of radio-induced laryngeal damage between 1990 and 1996 |

**Table 33 cont Descriptive characteristics of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Study location** | **Dates of enrolment** | **Number of patients** | **Number of males** | **Mean age**  **(years**± **SD)** | **Co-morbidities** | **Inclusion/Exclusion criteria** |
| Roden,  2001 | USA | Jul 1979 to  Sep 1987 | 13 | 7 | 63.3±8.6  Range: 46-75 | Radiation damage to areas of the brain outside the afferent visual system | Inclusion: All patients with presumed radiation damage to the optic nerves or chiasm that were referred to the Neuro- Ophthalmology service at Wills Eye Hospital Philadelphia, Pennsylvania  Exclusion: Patients were excluded from this report due to alternative explanations of visual loss including tumour mass contiguous with the intracranial optic nerves or chiasms, possible optic neuritis, possible malignant meningitis and occipital lobe radiation |
| Yu,  2002 | Taiwan | Jun 1998 to  May 1999 | 5 patients with 6 soft tissue injuries | 0 | 54±7.35  Range: 49-67 | NR | Inclusion: All patients with breast sequelae post irradiation between June 1998 and May 1999 referred to the hyperbaric oxygen centre of the Changhua Christian Hospital, Changhua |

Abbreviations: NR, not reported (ie unclear, not stated or unknown); COPD, chronic obstructive pulmonary disease

**Table 34 Descriptive characteristics of case series of HBOT in other radiation-induced complications**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Study location** | **Dates of enrolment** | **Number of patients** | **Number of males** | **Mean age**  **(years)** | **Co-morbiditiesa** | **Inclusion/Exclusion criteria** |
| Mayer,  2001 | Austria | Jun 1995 to  Mar 2000 | 18 | 18 | 71.2  Range: 64-77 years | . Diabetes (6)  . IgG-Kappa-plasmocytoma (1)  . Bladder cancer (1)  . Myelodysplasia (1)  . Amyloidosis (1) | Inclusion: All patients suffering from radiation induced proctitis and/or cystitis able to undergo HBO treatment at the Division of Thoracic and Hyperbaric surgery, Graz, Austria, between June  1995 and March 2000  Exclusion: Patients with severe emphysema and patients unable to achieve pressure adjustment in the middle ear |
| Woo,  1997 | Australia | NR | 18 | 17 | 72 both groupsb | NR | Inclusion: All patients completing a course of HBO therapy at the Fremantle Hospital Medicine Unit, Western Australia for radiation proctitis as assessed by proctoscope, sigmoidoscope, or colonoscope, and none had any concomitant bleeding disorder such as haemophilia |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

a Patients may have had more than one co-morbidity

b Insufficient data available to calculate other values

**Table 35 Validity characteristics of case series of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Explicit inclusion/exclusion criteriaa** | **Outcomes assessed in all patients** | **Uniform follow up** |  | **Measurement of outcomes** | **Outcomes quantified** | **Outcomes measured objectively** | **Blinded assessment of outcome** | **Indication/Disease severity uniform across patients** |
| Feldmeier,  1993 | Yes | No | No | NR |  | No | No | NR | Chandler grade IV (8)  Chandler grade III (1) |
| Feldmeier,  1995 | Yes | Yes | No | Wound healing | | No | NR | NR | Grade 3 radiation injury (2)  Grade 4 radiation injury (6) using the late radiation morbidity scoring system |
| Feldmeier,  1996 | Yes | Yes | NR | Wounds were healed, inadequate or did not heal | | No | NR | NR | All patients Grade 4 radiation injury using the late radiation morbidity scoring  system |
| Feldmeier,  2000 | Yes | Yes | No | Healed  Improved  Amputation required | | No  No  Yes | No  No  Yes | NR | No scoring system used. Description given of the size but not severity of the wounds |
| Flintisis  2000 | Yes | No | NR | Major improvement  Preservation of voice  Failed response to  HBOT  Total laryngectomy required | | No No No  No | No NR No  Yes |  | Chandler Grades III and IV |
| Roden,  2001 | Yes | No | Unclear | Vision Improvement  Visual acuity | | Yes  Yes | Yes  Yes | NR | Heterogenous patient group according to tests of visual status |
| Yu,  2002 | Yes | Yes | Yes | Recovered  Partially recovered  Pre/Post test TcPO2 | | No  No  Yes | No  No  Yes | NR | NR |

Abbreviations: NR, not reported (ie unclear, not stated or unknown); TcPO2, transcutaneous oxygen pressure

a Despite explicit inclusion criteria being given, the decision to refer to HBO therapy may have been biased, dependent upon the referring physician

**Table 36 Validity characteristics of case series of HBOT in other radiation-induced complications**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Explicit inclusion/exclusion criteriaa** | **Outcomes assessed in all patients** | **Uniform follow up** | **Measurement of outcomes** | **Outcomes quantified** | **Outcomes measured objectively** | **Blinded assessment of outcome** | **Indication/Disease severity uniform across patients** |
| Mayer,  2001 | Yes | Yes | No | Described as healed etc but not defined | No | NR | NR | NR |
| Woo,  1997 | Yes | Yes | No | Symptoms described as having improved, partially improved or completely improved | No | No | NR | NR |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Table 37 Treatment descriptions of case series of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Radiation dose (cGray)** | **Details of radiation therapy** | **Type/location of STRN** | **Time from radiation exposure to injury** | **Time from injury to HBOT** | **Therapies tried prior to**  **HBOT** | **HBOT regimen** | **Concomitant therapies** |
| Feldmeier,  2000 | 3,000-6,000 | NR | Extremities | 6 months to  17 years | Immediate to 3 years | NR | 100% oxygen at 2.4 ATA for 90 minutes (3x 30 minutes with 10 min air breaks)  Total number of sessions: 1-95 | 9/16 soft tissue-only patients underwent a surgical procedure All patients received daily wound care |
| Feldmeier,  1996 | 2,000-8,500 | NR | Abdominal wall (15) Groin (13)  Pelvic Bone (2) Perineum (7) Small bowel (1)  Skin of buttocks (1) Vagina (5) | Immediate to  53 years | Immediate to 2 years | Reconstructive surgeries:  5 prior to HBOT  3 at time of HBOT NR  NR NR NR | 100% oxygen at 2.4 ATA for 90 minutes, 6 days per week  Total number of sessions: 3-69 | Patient-specific daily wound care |
| Feldmeier,  1995 | 3,900-6,000 | NR | Chest Wall  Late radiation morbidity scoring system:  Grade 3 (2) Grade 4 (6) | Immediate to  7 years | Immediate to 23 years | NR | 100% oxygen at 2.4 ATA for 90 minutes  Total number of sessions: 7-33 | Patient-specific daily wound care Split thickness skin grafts and/or myocutaneous flaps (4) |
| Feldmeier,  1993 | 4,500-7,000 (Unit not specified) | NR | Laryngeal:  Chandler grade IV (8) Chandler grade III (1) | 3 months to 2 years | NR | NR | 100% oxygen at 2.4 ATA for  3x10 minutes exposure once daily, 6 days per week  Total number of sessions : 8-to  45 | NR |
| Flintisis  2000 | 5,000-7,545 | NR | Laryngeal:  Chandler Grade III (2) Chandler Grade IV (16) | 3 months to 3 years | NR | Symptomatic therapy as needed with parenteral antibiotics, steroids, racemic epinephrine, bronchodilators, and humidity before and after HBO therapy | 100% oxygen at 2 ATA for 2 hours twice daily, 6 days per week  Total number of sessions: 6-80 | Symptomatic therapy as needed with parenteral antibiotics, steroids, racemic epinephrine, bronchodilators and humidity before and after HBO therapy |

**Table 37 (cont) Treatment descriptions of case series of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Radiation dose (cGray)** | **Details of radiation therapy** | **Type/location of STRN** | **Time from radiation exposure to injury** | **Time from injury to HBOT** | **Therapies tried before**  **HBOT** | **HBOT regimen** | **Concomitant therapies** |
| Roden,  2001 | 4,500-7,200 | NR | Optic nerves or chiasm resulting in visual symptoms | 4 to 35 months | NR | NR | 100 % oxygen, pressure not reported  Total numbers of hours of HBOT:  18-160 (Data missing for one patient) | Corticosteroids (11/13) |
| Yu,  2002 | 5,040-6,600 | NR | Breast. Patients had a range of symptoms including:  . breast/chest wall painful oedema (4)  . axillary painful oedema with movement limitation (5)  . non-healing ulcer (1) | NR | NR | Standard treatment including surgical debridement and regular wound care | 100% oxygen at 2.5 ATA for 100 minutes (with a 5 minute air break every 30 minutes) daily, 6 days per week  Total number of sessions: 15-40 | NR |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Table 38 Treatment descriptions of case series of HBOT in other radiation-induced injuries**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Radiation dose (Gray)** | **Details of radiation therapy** | **Type/location of**  **STRN** | **Time from radiation exposure to injury** | **Time from injury to HBOT** | **Therapies tried before HBOT** | **HBOT regimen** | **Concomitant therapies** |
| Mayer,  2001 | 66/2 (2)a  70/2 (15) | Photon beams of 8 or 23  Megavolts  (Dose not reported) | Proctitis: 7  Cystitis: 8  Cystitis and proctitis: 3 | Occurrence of late GI  complications: median  7.75 months  Occurrence of late GU  complications:  median 15.84 months | NR | Bladder irrigation:  4 patients with cystitis  2 patients with both cystitis and proctitis  Intravesical agents:  2 patients with cystitis  1 patient with both cystitis and proctitis  Laser coagulation:  2 patients with proctitis  Local medicaments:  5 patients with proctitis  2 patients with both cystitis and proctitis  Systemic therapy:  1 patients with proctitis  2 patients with both cystitis and proctitis | 100% oxygen at 2.2 to 2.4  ATA for 60 minutes daily, 7 days per week.  Total number of sessions:  2-60  (Patients were to have received a minimum of 20 treatments) | NR |
| Woo,  1997 | >60  (Exact dose not reported) | Mega-voltage  X-rays (Dose not reported) | Proctitis | NR | Mean 20 months | Most had failed previous therapies including:  Steroids (13)  Local anaesthetic cream (3) Narcotics (1)  Zinc oxide gel (1) NSAIDs (1)  Massage and acupuncture for pain (1) | 100% oxygen at 2 ATA for  105-minute sessions daily, 6 days per week  Total number of sessions:  12-40 | NR |

Abbreviations: NR, not reported (ie unclear, not stated or unknown); GU, genitourinal

a Total dose. Radiotherapy was either limited to the prostate and seminal vesicles/prostate bed by using an anterior and two lateral fields or included the pelvic lymph nodes in four field box technique (504 Gray/1.8 Gray) followed by a boost in a three field technique

**Table 39 Results of case series of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |
| --- | --- | --- | --- |
| **First author, year** | **Outcomes reported** | **Result** | **Duration of follow-up** |
| Feldmeier,  2000 | Healed  Significantly Improved  Required amputation  Discharged to hospice (lung metastases) | 11/17 (65.0%)  1/17 (5.7%  4/17 (23.6%  1/17 (5.7%) | NR |
| Feldmeier,  1996 | Healed Inadequate Did not heal  Lost to follow up | 25/42 (59.5%)  10/42 (23.8%)  6/42 (14.3%)  1/42 (2.4%) | NR |
| Feldmeier,  1995 | Healed  Discontinued HBOT due to recurrent cancer | 6/8 (75.0%)  2/8 (25.0%) | NR |
| Feldmeier,  1993 | Laryngectomy required  Voice quality: Good  Slight hoarseness  Tracheostomies able to be decannulated Fistulae able to close without surgery Required surgery  Deaths:  Lung cancer 4 years post-treatment Ethanol Abuse 4 years post-treatment Respiratory arrest 2 years post-treatment Colon cancer 2 years post-treatment | None  7/9 (77.7%)  2/9 (22.3%)  3/3 (100.0%)  2/4 (50.0%)  2/4 (50.0%)  1/9 (11.1%)  1/9 (11.1%)  1/9 (11.1%)  1/9 (11.1%) | 2-10 years |
| Flintisis,  2000 | Major Improvement  Voice and deglutition in good or normal condition  Laryngectomy required | 13/18 (72.2%)  18/18 (100.0%)  0/18 (0.0%) | 5 months-4 years |

**Table 39 (cont) Results of case series of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |
| --- | --- | --- | --- |
| **First author, year** | **Outcomes reported** | **Result** | **Length of follow-up** |
| Roden,  2001 | Vision improvement  Visual acuity:  Remained within two lines of pre-treatment level  Lost vision in one eye  Lost visual acuity | 0/13 patients (26 eyes total)  18 eyes per 26 eyes total  1 eye per 26 eyes total  5 eyes per 26 eyes total | 1-4 years |
| Yu,  2002 | Recovered  Partially relieved  Local tissue oxygenation status | 4/5 (80%)  1/5 (20%) Pre test (range): 13-16  Post test (range): 43-67 | 2 years |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Table 40 Results of case series of HBOT in other radiation-induced injuries**

|  |  |  |  |
| --- | --- | --- | --- |
| **First author, year** | **Outcomes reported** | **Result** | **Length of follow-up** |
| Mayer,  2001 | Underwent adequate treatment  Significant Improvement  Improvement to level of no symptoms  Bleeding ceased  Ineffective treatment outcome  Went on to cystectomy | 16/18  GI, p=0.004; GU, p=0.004  4/18  5/5 proctitis, 6/8 cystitis  2/18  1/18 | 4.8-26.9 months |
| Woo,  1997 | Overall improvement in all symptoms  Bleeding:  . Mild, no transfusions  . Moderate  . Severe (>6 units in 3 months) Pain  Incontinence  Diarrhoea | NI PI CI  8 8 2  6 1 4  3 1 0  1 1 0  2 1 1  1 1 2  4 2 2 | 3-65 months |

Abbreviations: GI, gastrointestinal; GU, genitourinal; NI, no improvement; PI, partial improvement; CI, complete improvement

# Appendix F3

**Non-healing, refractory wounds in non-diabetic wounds: case series considered on expert advice**

**Table 41 Descriptive characteristics of case series of HBOT in non-healing, refractory wounds in non-diabetic patients**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Study location** | **Dates of enrolment** | **Number of patients** | **Number of males** | **Mean age**  **(years)** | **Co-morbiditiesa** | **Inclusion/Exclusion criteria** |
| Cianci,  1988a | USA | Jan 1983 to Jul  1987 | 39, including 19 with diabetes | NR | 67 | Not reported | Inclusion: Patients who had serious lesions of the lower extremities which had been refractory to standard medical or surgical treatment and who had previously undergone treatment with HBOT. Patients had to have a non- healing lesion after at least two months of standard therapy and were assessed for blood flow, rehabilitation potential and the ability to cooperate in an aggressive wound care program |

a It was unclear whether the study enrolled consecutive patients. Results were not presented separately for diabetics and non-diabetics

**Table 42 Schedules used in case series of HBOT in non-healing, refractory wounds in non-diabetic patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Type and location of wound** | **Time from wound/lesion to HBOT** | **Therapies tried before HBOT** | **Duration of therapy tried before HBOT** | **HBOT regimen** | **Concomitant therapies** |
| Cianci,  1988 | Lesions of the lower limb | NR | Standard therapy (not defined) | ≥ 2 months | 100% oxygen at 2  ATA for 1.5 to 2 hours once or twice daily | Patients were treated by a multidisciplinary team of medical specialists in the setting of aggressive wound care consisting of wound perfusion assessments; early surgical revascularisation; daily or twice daily wound inspection, dressing changes, and debridement; avoidance of topical toxins; maintenance of nutritional and metabolic control; antibiotic administration based on culture results |

**Table 43 Validity characteristics of case series of HBOT in non-healing, refractory wounds in non-diabetic patients**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Explicit inclusion/exclusion criteria** | **Outcome measured n all enrolled patients** | **Uniform follow-up** | **Measurement of outcomes** | **Outcomes quantified** | **Outcomes measured objectively** | **Blinded assessment of outcome** | **Indication/disease severity uniform across patients** | **Description given of failed treatment** |
| Cianci,  1988 | Yes | Yes | NR | NR | Some | Some | NR | NR | NR |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Table 44 Results of case series in HBOT in non-healing, refractory wounds in non-diabetic patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **First author, year** | **Outcomes reported** | **Result** | **Length of follow-up** |
| Cianci,  1988a | Vascular surgery  Length of stay  Mean number of HBOT treatments  Mean HBOT cost  Total hospital charges  Successful salvage | 20/39 (51%)  30 days  31  US$10,368  US$29,709  36/39 (92%) | Not reported |

a Combined results for 19 diabetic patients and 20 non-diabetic patients, total 39

# Appendix F4

**Refractory soft tissue radiation injuries: case series considered on expert advice**

**Table 45 Descriptive characteristics of case series of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Study location** | **Dates of enrolment** | **Number of patients** | **Number of males** | **Mean age**  **(years)** | **Co- morbiditiesa** | **Inclusion/Exclusion criteria** |
| Bevers,  1995 | The  Netherlands | Jan 1986 to Jan  1984 | 40 | 27 | 71.4  Range: 56-86 | NR | Inclusion: Patients with severe haemorrhagic cystitis due to radiotherapy not responding to other treatments  Exclusion: Patients with evidence of tumour recurrence in the bladder at cystoscopy, the presence of concomitant bleeding disorders, and/or severe pulmonary disease with pulmonary bullae |
| Lee  1994 | Taiwan | Nov 1989 to  Jan 1996 | 40 | 3 | 63±9 (SD) Range: 42-82 | NR | Inclusion: Patients with haemorrhagic radiation cystitis |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Table 46 Validity of case series of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Explicit inclusion/exclusion criteria** | **Outcomes assessed in all patients** | **Uniform follow up** | **Measurement of outcomes** | **Outcomes quantified** | **Outcomes measured objectively** | **Blinded assessment of outcome** | **Indication/disease severity uniform across patients** |
| Bevers,  1995 | Yes | Yes | No | Recurrence of severe haematuria, cystectomy, or death | Yes | Yes | No | No |
| Lee,  1994 | No | Yes | No | Recurrence of gross haematuria, cystoscopic findings | No | No | No | NR |

**Table 47 Treatment descriptions of case series of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Radiation dose (Grays)** | **Radiation regimen** | **Type/ location of injury** | **Time from radiation exposure to injury** | **Time from injury to HBOT** | **Therapies tried before HBOT** | **HBOT regimen** | **Concomitant therapies** |
| Bevers,  1995 | Mean: ≥52 | NR | Bladder | Mean: 53.1 months  Range: 4-253 | NR | Clot evacuation and electrocoagulation: (40) Tranexamic acid: (12)  Alum: (11) Corticosteroids: (3) Neomycin: (1) Etoglucide: (1) Propantheline: (1) Silver nitrate: (1) Unspecified: (17)  Most required multiple blood transfusions, mean  8.2 units | 100% oxygen inhaled at 3 bars for daily sessions of 90 minutes in a multiplace chamber, 5 to 6 times a week  Total number of sessions: 20 | NR |
| Lee, 1994 | 63±(11) Range: 50-90 | NR | Bladder | Mean: 9.1 years±5.25 (SD)  Range: 2-26 | NR | NR | 100% oxygen by mask at 2.5 ATA for  100 minutes in a multiplace chamber | NR |

Abbreviations: NR, not reported (ie unclear, not stated or unknown)

**Table 48 Results of case series of HBOT in refractory soft tissue radiation injuries**

|  |  |  |  |
| --- | --- | --- | --- |
| **First author, year** | **Outcomes reported** | **Result** | **Length of follow-up** |
| Bevers,  1995 | Overall recurrence rate  No haematuria for three months following treatment  Occasional, slight haematuria  No effect | 0.12 per year  30/40 (75%)  7/40 (17.5%)  3/40 (7.5%) | Median: 13 months |
| Lee,  1994 | Resolution of haematuria  “Marked decrease” in haematuria | 33/40 (82.5%)  3/40 (7.5%) | Mean: 21 months±12 (SD) Range: 3-49 |

# Appendix G

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# Abbreviations

AETMIS Agence d’Évaluation des Technologies et des Modes d’Intervention en

Santé (Health technology agency based in Quebec) ATA atmosphere absolute

CRD Centre for Reviews and Dissemination

GIT Groninger Intelligence Test HBOT hyperbaric oxygen therapy HBO hyperbaric oxygen

HTA health technology assessment

ICD-10-AM International Classification of Disease, 10th edition, Australian

Modification.

LND lymph node dissection

MBS Medicare Benefits Schedule

MeSH medical subject heading

MSAC Medical Services Advisory Committee

NCCAM National Centre for Complementary and Alternative Medicine (USA) NHLBI National Heart, Lung, and Blood Institute (USA)

NHMRC National Health and Medical Research Council

NHS National Health Service (UK) Pa pascal

SF-36 Short Form 36

RCT randomised controlled trial

WAIS Wechsler Adult Intelligence Scale

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