Hyperbaric oxygen therapy for late radiation tissue injury (Review)

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[Intervention Review]

Hyperbaric oxygen therapy for late radiation tissue injury

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ABSTRACT

Background

Cancer is a significant global health problem. Radiotherapy is a treatment for many cancers and about 50% of patients having radiotherapy with be long-term survivors. Some will experience late radiation tissue injury (LRTI) developing months or years later. Hyperbaric oxygen therapy (HBOT) has been suggested as a treatment for LRTI based upon the ability to improve the blood supply to these tissues. It is postulated that HBOT may result in both healing of tissues and the prevention of problems following surgery.

Objectives

To assess the benefits and harms of HBOT for treating or preventing LRTI.

Search methods

In March 2011 we updated the searches of the Cochrane Central Register of Controlled Trials (CENTRAL), (*The Cochrane Library*, Issue 1), MEDLINE, EMBASE, DORCTIHM and reference lists of articles.

Selection criteria

Randomised controlled trials (RCTs) comparing the effect of HBOT versus no HBOT on LRTI prevention or healing.

Data collection and analysis

Three review authors independently evaluated the quality of the relevant trials using the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* and extracted the data from the included trials.

Main results

Eleven trials contributed to this review (669 participants). For pooled analyses, investigation of heterogeneity suggested important variability between trials but there was some evidence that HBOT is more likely to achieve mucosal coverage with osteoradionecrosis (ORN) (risk ratio (RR) 1.3; 95% confidence interval (CI) 1.1 to 1.6, P = 0.003, number needed to treat for an additional beneficial outcome (NNTB) 5). From single studies there was a significantly increased chance of improvement or cure following HBOT for radiation proctitis (RR 1.72; 95% CI 1.0 to 2.9, P = 0.04, NNTB 5), and following both surgical flaps (RR 8.7; 95% CI 2.7 to 27.5,

P = 0.0002, NNTB = 4) and hemimandibulectomy (RR 1.4; 95% CI 1.1 to 1.8, P = 0.001, NNTB 5). There was also a significantly improved probability of healing irradiated tooth sockets following dental extraction (RR 1.4; 95% CI 1.1 to 1.7, P = 0.009, NNTB 4).

There was no evidence of benefit in clinical outcomes with established radiation injury to neural tissue, and no data reported on the use of HBOT to treat other manifestations of LRTI. These trials did not report adverse effects.

Authors' conclusions

These small trials suggest that for people with LRTI affecting tissues of the head, neck, anus and rectum, HBOT is associated with improved outcome. HBOT also appears to reduce the chance of ORN following tooth extraction in an irradiated field. There was no such evidence of any important clinical effect on neurological tissues. The application of HBOT to selected patients and tissues may be justified. Further research is required to establish the optimum patient selection and timing of any therapy. An economic evaluation should be undertaken.

PLAIN LANGUAGE SUMMARY

Hyperbaric oxygen therapy (HBOT) for the treatment of the late effects of radiotherapy

There is a risk of serious complications developing after radiation treatment for cancer (late radiation tissue injury (LRTI). HBOT involves breathing oxygen in a specially designed chamber. It is used as a treatment to improve oxygen supply to damaged tissue and stimulate healing.

We found some evidence that LRTI affecting the head, neck and lower end of the bowel can be improved with HBOT. There is little evidence for or against benefit in other tissues affected by LRTI. Our conclusions are based on 11 randomised trials with a limited number of patients. Further research is needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Hyperbaric oxygen therapy for late radiation tissue injury

Patient or population: patients with late radiation tissue injury
Settings: inpatients and outpatients in a hyperbaric facility
Intervention: hyperbaric oxygen therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	hyperbaric oxygen therapy				
Complete mucosal cover in patients with osteoradionecrosis Physical examination Follow-up: 12 to 18 months	**Low-risk population**		**RR 1.3** (1.1 to 1.6)	246 (3 studies)	⊕⊕⊕⊕ **high**[1,2]	
	550 per 1000	**715 per 1000** (605 to 880)				
	Medium-risk population					
	650 per 1000	**845 per 1000** (715 to 1000)				
	High-risk population					
	750 per 1000	**975 per 1000** (825 to 1000)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] One included study was reported only in a textbook chapter
[2] The NNTB for healing with HBOT is only 5 (95% CI 3 to 12) for this serious problem

BACKGROUND

Description of the condition

Cancer is a significant global health problem. According to World Health Organization (WHO) statistics, more than 10 million people are diagnosed with cancer every year, and it is estimated there will be 15 million new cases every year by 2020. Cancer causes 6 million deaths every year or 12% of deaths worldwide (WHO 2004). Radiotherapy is a well-established treatment of suitable malignancies in a wide variety of anatomical areas. Of the approximately 1.2 million new cases of invasive cancer diagnosed annually in the USA, for example, about 50% will receive radiotherapy (Jemal 2002), and of these, about 50% will be long-term survivors. While radiotherapy may acutely injure any normal tissue in the path of the radiation, this acute injury generally resolves following completion of the treatment course. Serious, radiation-related complications developing months or years after radiation treatment, collectively known as late radiation tissue injury (LRTI), are relatively rare and will significantly affect between 5% and 15% of those long-term survivors who received radiotherapy, although the incidence varies widely with dose, age and site (Rubin 1968; Stone 2003; Thompson 1999; Waddell 1999). Although any tissue may be affected, LRTI is in practice most common in the head and neck, chest wall, breast and pelvis - reflecting the anatomical areas most commonly irradiated and the likelihood of survival for patients treated for cancer at these anatomical sites.

When LRTIs occur, tissues undergo a progressive deterioration characterised by a reduction in the density of small blood vessels (reduced vascularity) and the replacement of normal tissue cells with dense fibrous tissue (fibrosis), until there is insufficient oxygen supplied to sustain normal function. This situation is frequently exacerbated by secondary damage due to infection or surgery in the affected area (Rubin 1984). This progressive and delayed radiation damage may reach a critical point where the tissue breaks down to form an ulcer or area of cell death (radiation necrosis, or radionecrosis). LRTI can affect any organ system, although some tissues are more sensitive to radiation effects than others (Thompson 1999; Trott 1984; Waddell 1999).

Historically, the management of these injuries has been unsatisfactory. LRTI may be life threatening and may significantly reduce quality of life (QoL). Conservative treatment is usually restricted to symptom management, while definitive treatment traditionally entails surgery to remove the affected part and extensive repair (Stone 2003). Surgical intervention in an irradiated field is often disfiguring and associated with an increased incidence of delayed healing, breakdown of a surgical wound or infection.

Description of the intervention

Hyperbaric oxygen therapy (HBOT) has been proposed to improve tissue quality, promote healing and prevent breakdown of irradiated tissue fields. It may be defined as the therapeutic administration of 100% oxygen at environmental pressures greater than 1 atmosphere absolute (ATA). Administration involves placing the patient in an airtight vessel, increasing the pressure within that vessel, and giving 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased pressure of oxygen to the lungs, blood and tissues. Typically, treatments involve pressurisation to between 2.0 and 2.5 ATA for periods between 60 and 120 minutes once or twice daily to a total of 30 to 60 sessions of treatment.

How the intervention might work

The intermittent application of HBOT is the only intervention that has been shown to increase the number of blood vessels in irradiated tissue. This has been demonstrated by Marx in a rabbit mandibular (jaw bone) model and further confirmed by serial tissue oxygen level measurements using electrodes placed on the overlying skin (transcutaneous oximetry) in humans undergoing a course of therapy for radiation necrosis of the mandible (Marx 1988; Marx 1990). In the rabbit study, the jaw and surrounding soft tissues were heavily irradiated and one group 'rescued' with HBOT 6 months later. The two control groups showed no improvement while a series of 20 sessions at 2.4 ATA on 100% oxygen returned the density of blood vessels to 80% of normal. In the human study, a progressive recovery of low transcutaneous oximetry readings into the normal range was achieved in a group of patients receiving therapy for underlying osteoradionecrosis (ORN) (radiation necrosis of bone).

HBOT seems most likely to achieve such improvements through a complex series of changes in affected tissues. Tissue swelling is probably improved through an osmotic effect of oxygen, while the establishment of a steep oxygen gradient across an irradiated tissue margin is a powerful stimulus to the growth of new blood vessels (Davis 1988; Hills 1999). In addition, improving oxygen levels will improve white cell and fibroblast function, further enhancing wound healing (Mandell 1974). Improved tissue quality has been demonstrated in a model of radiation small bowel injury (Feldmeier 1995; Feldmeier 1998).

Why it is important to do this review

While HBOT has been used for LRTI since at least 1975 (Mainous 1975), most clinical studies have been limited to relatively small case series or individual case reports. There have been relatively few comparative studies published, and no previous quantitative systematic reviews of which we are aware. In a semi-quantitative review, Feldmeier and Hampson located 71 such reports involving a total of 1193 patients across eight different tissues (Feldmeier 2002). In these patients, for whom conservative treatment had failed to improve symptoms, there were clinically significant im-

provements in the majority of patients. Results varied between tissue types, with neurological tissue appearing the most resistant to improvement. Only 7 of 71 reports indicated a generally poor response to HBOT. The present review will complement Feldmeier 2002 by using explicit Cochrane methodology to locate, quantitatively appraise and summarise the comparative data, while not discussing in any detail the non-comparative series summarised in that review.

HBOT is associated with some risk of adverse effects including damage to the ears, sinuses and lungs from the effects of pressure; temporary worsening of short sightedness (myopia); claustrophobia and oxygen poisoning. Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention. It has further been suggested that HBOT may increase the incidence and rate, or both, of growth of tumours in patients with a history of malignancy. One comprehensive review fails to support these concerns (Feldmeier 2003).

OBJECTIVES

The objectives of this review were to determine the efficacy and safety of HBOT in the treatment of patients with LRTI.

Specifically we addressed the following questions:

- Is a course of HBOT more efficacious than placebo or no treatment in improving symptoms, signs and disability for patients with LRTI?
- Is a course of HBOT more efficacious than placebo or no treatment in preventing further deterioration for patients with LRTI?
- Is HBOT administration safe?

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and pseudo-RCTs that compared the effect of a regimen including HBOT on any form of LRTI, with any treatment regimen not including HBOT.

Types of participants

Any person with LRTI (including necrosis) of whatever tissue. We also accepted patients treated with large-dose radiotherapy likely to induce relatively early necrosis (e.g. radiosurgery to a brain lesion).

Types of interventions

We accepted trials comparing regimens that included HBOT with similar regimens that excluded HBOT. Where co-interventions differed significantly between studies this was clearly stated and the implications discussed.

The intervention under examination was HBOT administered in a compression chamber between pressures of 1.5 ATA and 4.0 ATA and treatment times between 30 minutes and 120 minutes daily or twice daily. These parameters exclude trivial treatments on the one hand, and highly toxic exposures on the other. The comparator group was diverse, and we accepted any standard treatment regimen designed to promote tissue healing or prevent further deterioration.

Types of outcome measures

Appropriate outcome measure depended on the nature of the LRTI and the anatomical location. Studies were eligible for inclusion if they reported any of the following outcome measures:

All anatomical areas

Primary outcome measures:

1. Survival
2. Complete resolution of necrosis or tissue damage
3. Complete resolution or substantial improvement of necrosis or tissue damage
4. Improvement in LENT-SOMA (Late Effects Normal Tissues - Subjective, Objective, Management, Analytic) scale (The LENT-SOMA scales were developed jointly by the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) in 1995 in order to standardise assessment of LRTI (Pavy 1995). Scales are location specific and have been summarised in a number of forms for each location. The implications for pooling are discussed as required. The scale dimensions are summarised in Table 1.)

Secondary outcome measures:

1. Resolution of pain
2. Resolution of swelling
3. Improvement in QoL, function or both

Osteoradionecrosis (ORN)

Primary outcome measures:

1. Healing with complete soft tissue coverage over bone
2. Resolution of sinus tract between bone and skin or mucosa
3. Resolution of fracture or re-establishment of bony continuity

4. Development of ORN in tooth socket following extraction or following implant

Secondary outcome measures:

- Improvement in X-ray appearance

Head and neck soft tissues

Primary outcome measures:

1. Wound dehiscence (breakdown of a surgical wound)
2. Surgical removal of larynx
3. Major vessel bleeding

Secondary outcome measures:

1. Speed of wound healing
2. Improvement in swelling or 'woodiness' of tissue
3. Reversal of tracheostomy (surgical breathing hole in the trachea)

Urinary bladder

Primary outcome measures:

1. Resolution of bleeding
2. Removal of bladder and urine diversion procedures

Secondary outcome measures:

1. Improved cystoscopic appearance
2. Frequency
3. Dysuria (pain on passage of urine)

Chest wall

- Nil additional to those listed under 'All anatomical areas'.

Bowel

Primary outcome measures:

1. Resolution of bleeding
2. Operations on the bowel such as colostomy, ileostomy or bowel resection

Secondary outcome measures:

- Improvement in pain score

Neurological tissue

Primary outcome measures:

1. Improvement in objective motor function
2. Improvement in visual acuity

Secondary outcome measures:

1. Improvement in sensory function
2. Improvement in functional ability or activities of daily living (ADL)
3. Improvement in neuropsychiatric testing
4. Improvement in X-ray or scan appearance
5. Reduction in steroid dose

Extremities

- Nil additional to those listed under 'All anatomical areas'.

Adverse events of HBOT

1. Recurrence of tumour (locally or remote)
2. Visual disturbance (short and long term)
3. Damage from pressure (aural, sinus or pulmonary barotrauma, in the short and long term)
4. Oxygen toxicity (short term)
5. Withdrawal from treatment for any reason
6. Any other recorded adverse effect

Search methods for identification of studies

Electronic searches

It was our intention to capture both published and unpublished studies.

Initial searches were made in June 2005 and repeated in August 2008 and March 2011.

We searched the following (from inception) in November 2004 and then repeated the searches in September 2008 and March 2011: the Cochrane Central Register of Controlled Trials (CENTRAL Issue 1 2011) on *The Cochrane Library*, MEDLINE (1966 to week 1, March 2011), EMBASE (1980 to week 11, 2011), EBSCO CINAHL (1982 to 2008) and an additional database developed in our Hyperbaric facility, DORCTIHM (The Database of Randomised Trials in Hyperbaric Medicine, Bennett 2011 - searched March 2011). The DORCTHIM search was by the keywords 'coronary or cardiac or heart or myocard$' and and 'hyperbaric oxygen$'. CINAHL was searched in 2004 and 2008 but not 2011. The search strategies for other databases were broad and the search strategies are given in Appendix 1, Appendix 2, Appendix 3, Appendix 4 and Appendix 5.

Searching other resources

- Experts in the field and leading hyperbaric therapy centres (as identified by personal communication and searching the Internet) were contacted and asked for additional relevant data in terms of published or unpublished randomised trials.
- Handsearch of relevant hyperbaric textbooks (Jain 2009, Kindwall 2008, Mathieu 2006, Neuman and Thom 2008), journals (*Undersea and Hyperbaric Medicine*, *Hyperbaric Medicine Review*, *Diving and Hyperbaric Medicine*, *Space and Environmental Medicine Journal*) and conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society, International Congress of Hyperbaric Medicine) published since 1980.
- Contacted of authors of relevant studies to request details of unpublished or ongoing investigations.
- Examination of the reference list of all trials for inclusion in this review.

All languages were considered. Authors were contacted if there was any ambiguity about the published data.

Data collection and analysis

Selection of studies

One review author (MB) was responsible for handsearching and identification of appropriate studies for consideration and all possibly relevant studies were entered into a bibliographic software package (Review Manager). Three review authors (MB, JF and NH) then examined the electronic search results and identified comparative studies that may have been relevant. Studies were retained when one or more review authors identified them as appropriate. Retained studies were retrieved in full and reviewed independently by three review authors, all with content expertise in HBOT, one with content expertise in radiation oncology (JF). In addition one of the review authors (MB) has expertise in clinical epidemiology. The review authors recorded data using the data extraction form developed for this review.

Data extraction and management

Each review author independently extracted the relevant data. Primary authors were contacted to provide information when missing data was encountered or if necessary data such as adverse events were not clearly stated. All differences were resolved by discussion among the review authors and no disputed trials required referral to the Review Group contact editor for appraisal. Review authors recorded data using the data extraction form developed for this review.

Assessment of risk of bias in included studies

We appraised each included study to assess the risk of bias as outlined in Section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
We appraised each included study according to the criteria described below. 'Unclear risk' means that insufficient information was available to make a judgement.

Random sequence generation (selection bias)

- Low risk: adequate sequence generation was reported using random number tables, computer random number generator, coin tossing or card/envelope shuffling.
- High risk: used a system involving dates, names or admittance numbers for the allocation of participants. We considered such studies as quasi-randomised and excluded them from the review.
- Unclear risk: did not describe one of the adequate methods but mentioned randomisation.

Allocation concealment (selection bias)

- Low risk: a randomisation method was described that would not allow an investigator/participant to know or influence allocation to an intervention group before an eligible participant entered the study, such as central randomisation or serially numbered, opaque, sealed envelopes.
- High risk: an inadequate method of allocation was used, such as alternate medical record numbers or unsealed envelopes; or there was information in the study report indicating that investigators or participants could have influenced group allocation.
- Unclear risk: the trial report mentioned randomisation but there was no information on the method used, or a method was reported that was not clearly adequate.

Blinding of participants (performance bias and detection bias)

We graded this item as 'Yes' for blinding participants, 'Unclear' if the relevant information was not stated in the trial report and 'No' for unblinded participants.

Blinding of outcome assessors (performance bias and detection bias)

We graded this item as 'Low risk' for blinded outcome assessment, 'Unclear' if the relevant information was not stated in the trial report and 'High risk' for any statement indicating unblinded outcome assessment.

- Incomplete outcome data addressed (description of withdrawals).
- Low risk: numbers of withdrawals per group with reasons provided; or clear from report that there were no withdrawals.

- High risk: some withdrawal evident but numbers per group and reasons not provided.
- Unclear risk: unclear from trial report whether there were any withdrawals.

Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)

We defined ITT analysis as being conducted when all trial participants were analysed in the group to which they were randomised regardless of which (or how much) of the treatment they actually received, and regardless of other protocol irregularities, such as ineligibility.

- Low risk: trial report stated that ITT was undertaken and this was confirmed on study assessment, or not stated but evident from study assessment that ITT was undertaken.
- High risk: ITT not confirmed on study assessment (participants who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation) regardless of whether analysis described as ITT.
- Unclear risk: described as ITT analysis, but unable to confirm on study assessment, or not reported and unable to confirm by study assessment.

Selective reporting

We defined selective reporting as whether all outcomes detailed in an original trial protocol were presented in the published report as follows:

- Low risk: all outcomes in trial protocol are reported
- High risk: only certain outcomes from the original protocol (for example outcomes with a statistically significant beneficial effect) are reported
- Unclear risk: full trial protocol not available (from study investigators or a trials register)

In the absence of the availability of a full trial protocol for any included report, we noted whether the results section of the published report presented results for all outcomes that were described in the methods section.

Any other risk of bias

Measures of treatment effect

It was our intention where possible to analyse the data from different anatomical sites together (see outcomes listed under 'all anatomical areas'). However, many outcomes are specific to a particular anatomical site, and these outcomes were analysed separately. All comparisons were made using an ITT analysis where possible and reflect efficacy in the context of randomised trialling, rather than true effectiveness in any particular clinical context. While we planned to compare survival over time using the log hazard ratio and variance (Parmar 1998), no suitable data were available. For dichotomous outcomes risk ratios (RRs) were used. For continuous data, the mean difference (MD) between treatment and control groups in each trial was calculated and aggregated using inverse variance weights to estimate an overall MD and its 95% confidence interval (CI). We used a fixed-effect model where there was no evidence of significant clinical heterogeneity between studies (see below), and employed a random-effects model when such heterogeneity was likely. All statistical analysis was performed using RevMan software.

Where co-interventions differed significantly between studies this was clearly stated and the implications discussed.

Overall primary outcomes (all anatomic areas)

1. Survival. For each trial, we calculated the RR for survival in the HBOT group compared to the control group. These RRs were pooled in a meta-analysis to estimate an overall RR and its 95% CI. A statistically significant difference between experimental intervention and control intervention was assumed if the 95% CI of the RR did not include the value 1.0. As an estimate of the clinical relevance of any difference between experimental intervention and control intervention, we calculated the number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) with 95% CI as appropriate, using the formula NNTB = 1/risk difference (RD) with 95% CI calculated from the 95% CI of the RR, following the method recommended in Altman 2001.
2. Complete resolution of necrosis or tissue damage. The RR for complete resolution of necrosis or tissue damage with and without HBOT was calculated using the methods described in (1) above.
3. Improvement in LENT-SOMA scales. For each trial, the MD in this score between HBOT and control groups was to be calculated and combined in a meta-analysis to estimate an overall MD and its 95% CI. No trials reported this outcome.

Overall secondary outcomes

- Radiological improvement. Statistical analysis would depend on the nature of the data, but would have followed the methods outlined above. No trials reported this outcome.

The outcomes for each anatomical site will be approached in an analogous manner to that outlined above.

- Adverse events. For each trial, we planned to calculate the RR for each adverse event in the HBOT compared to the control group. These RRs were to be pooled in a meta-analysis to estimate an overall RR and its 95% CI. No trials reported this outcome.

Dealing with missing data

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

Assessment of heterogeneity

Heterogeneity was assessed using the I^2 statistic and consideration given to the appropriateness of pooling and meta-analysis.

Subgroup analysis and investigation of heterogeneity

We considered subgroup analysis based on:

- anatomical location
- dose of oxygen received (pressure, time and length of treatment course)
- nature of the comparative treatment modalities
- severity of injury

Sensitivity analysis

We intended to perform sensitivity analyses for missing data and study quality based on the presence or absence of a reliable random allocation method, concealment of allocation and blinding of participants or outcome assessors where appropriate.

RESULTS

Description of studies

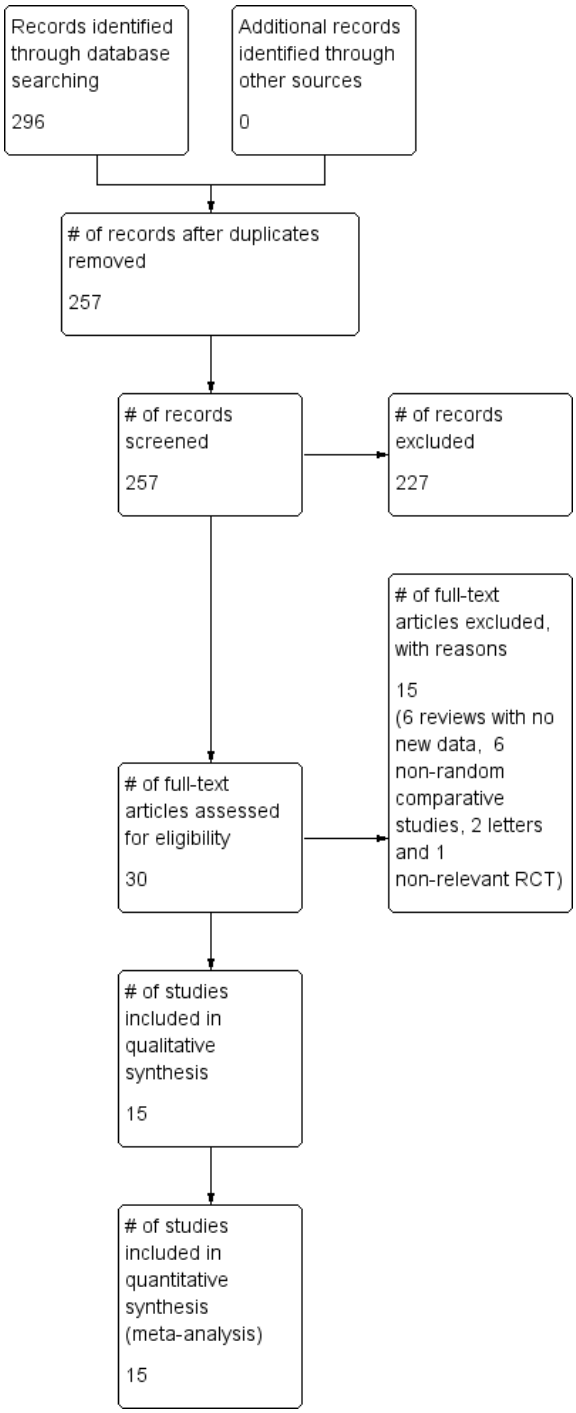
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Following our updated search in August 2008, we had identified a total of 116 publications apparently dealing with the use of HBOT for the treatment of LRTI. On the basis of screening the titles and abstracts, we excluded 98 records. The remaining 18 reports were retrieved in full text. After appraisal of the full reports we further excluded five reports with non-random controls (Carl 2001; Gal 2003; Granstrom 1999; Maier 2000; Niimi 1997), two systematic reviews (Coulthard 2002; Denton 2002) with no further randomised data and one randomised trial with no quantitative data (Tobey 1979). See table 'Characteristics of excluded studies'. The remaining 10 records describing eight studies were included in the review (Annane 2004; Clarke 2008; Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Pritchard 2001; Sidik 2007). Marx 1999a and Marx 1999b are trials reported for the first time in a textbook. The recruitment period for these studies is not known. As of August 2008, we had not been able to obtain a full-text copy of Sidik 2007, but this study has now been moved from 'Characteristics of studies awaiting classification' to 'Characteristics of included studies'.

Our most recent searches in March 2011 retrieved 180 records. After removal of duplicates, 145 records remained. On the basis of screening the titles and abstracts, we excluded 132 records. The remaining 13 papers were retrieved in full text. Of these reports, four were included (two studies, two secondary reports with new data). The nine excluded reports were added to the table 'Characteristics of excluded studies'.

The results of all three searches are combined and summarised in Figure 1. In total we have included 15 reports of 11 trials (Annane 2004; Clarke 2008; Gothard 2010; Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Pritchard 2001; Schoen 2007; Sidik 2007; Teguh 2009). During the search, we also discovered web-based announcements of two new trials planned in this area (HOPON 2011, a study of the prevention of ORN in the mandible; DAHANCA 2011 a study of the treatment of ORN in the mandible. These are now included in 'Characteristics of studies awaiting classification'.

Figure 1. Study flow diagram.



The included trials were published between 1985 and 2010, and the reviewers remain aware there is a large, multicentre trial underway into the effect of HBOT on six further different manifestations of LRTI. Clarke 2008 is the report of one group of that trial (radiation proctitis). In total, the included trials have data on 669 participants, 343 receiving HBOT and 326 control (see 'Characteristics of included studies').

These trials enrolled more females than males (Pritchard 2001 and Gothard 2010 enrolled 34 and 58 participants respectively, all female; Hulshof 2002 six females and one male; Clarke 2008 106 females and 13 males). Annane 2004, Schoen 2007, and Teguh 2009 enrolled more males (88 males, 25 females in total). All trials required radiotherapy to have been given prior to enrolment, but the dose and any accompanying chemotherapy varied considerably between studies. Prior exposure to a minimum of 64 Gy in the area under investigation was required by Marx (Marx 1999a; Marx 1999b), Teguh 2009 accepted patients with 46 to 70 Gy, but all other studies did not specify a minimum dose. Annane 2004 excluded those with more advanced disease. Clarke 2008 entered participants with radiation proctitis; Marx 1999a, Marx 1999b and Annane 2004 those with established ORN of the mandible; Hulshof 2002 those with cognitive deficits following brain irradiation with at least 30 Gy and both Pritchard 2001 and Gothard 2010 enrolled patients with radiation-induced brachial plexus lesions and arm lymphoedema respectively following irradiation of the breast. The other three trials treated patients without radiation tissue necrosis: Marx 1985 enrolled participants requiring tooth extraction in an irradiated field, Teguh 2009 treated irradiated patients with head and neck lesions before they developed LRTI and Schoen 2007 treated patients having dental implants in an irradiated area (see 'Characteristics of included studies').

Both the dose of oxygen per treatment session and for the total course of treatment varied between studies. The lowest pressure administered was 2.0 ATA (Clarke 2008) and the highest was 3.0 ATA (Hulshof 2002), while all other trials utilised 2.4 or 2.5 ATA. The duration of all treatments was 80 to 90 minutes. All trials administered a total of 30 treatments except Annane 2004 and Clarke 2008, where some individuals received 40 treatments. Annane 2004 used a twice daily treatment schedule.

There were no active comparator regimens administered to the control groups but withheld from the HBOT group of these trials. Three trials administered a blinded sham therapy (Annane 2004; Clarke 2008; Pritchard 2001) Details are given in 'Characteristics of included studies'.

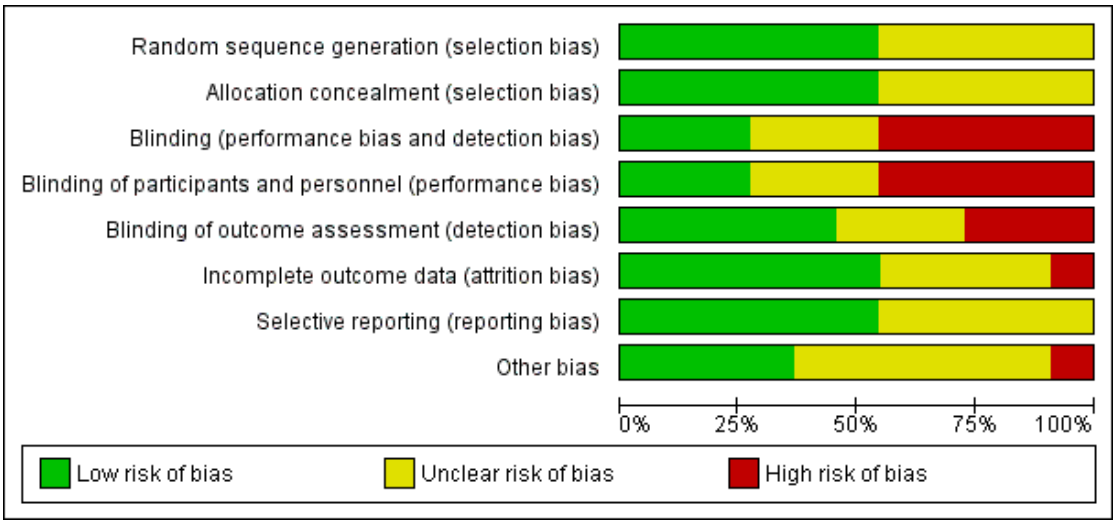
The follow-up periods varied from immediately after therapy (Clarke 2008), to 3 weeks following the treatment course (Marx 1999b), 6 months (Hulshof 2002; Marx 1985) and 1 year (Annane 2004; Gothard 2010; Pritchard 2001; Schoen 2007; Teguh 2009). Marx 1999a did not specify the time at which outcome was measured. All included studies reported at least one clinical outcome of interest. Of the outcomes identified above, these trials reported data on primary outcomes (resolution of problem, bony continuity established, mucosal cover, wound dehiscence and LENT-SOMA scale) and secondary outcomes (oedema resolution, pain scores, QoL, physical functioning, sensory function and neuropsychiatric testing).

Other outcomes (including non-clinical) reported included: radiological changes (Annane 2004), self-rated memory and dexterity (Hulshof 2002), sensory action potentials (Pritchard 2001), post-surgical complication rate (Marx 1999a), wound infection rate (Marx 1999b), assessment of lymphoedema (lymphoscintigraphy and dielectric constant) (Gothard 2010) and implant loss (Schoen 2007).

Risk of bias in included studies

Details of the quality assessment are given in 'Characteristics of included studies'. Study quality varied widely, however, because very few analyses could be pooled, study quality was not used as a basis for sensitivity analysis. The risk of bias for each study is presented graphically in Figure 2.

Figure 2.



Allocation concealment

Allocation concealment was adequately described in five studies (Annane 2004; Clarke 2008; Gothard 2010; Hulshof 2002; Pritchard 2001), all used a remotely located randomisation officer. For none of the remaining studies is there a clear indication that the investigators were unable to predict the prospective group to which a participant would be allocated.

Randomisation

Randomisation procedures were described in four studies (Annane 2004; Clarke 2008; Gothard 2010; Pritchard 2001), all employing a computer-generated random number table, but not in the other six.

Subject baseline characteristics

Given the variation in pathology outlined in 'Description of Studies' above, it is not surprising that there is considerable variation in patient baseline characteristics. Two studies did not specify any baseline characteristics except prior exposure to 6400 cGy in the area under investigation (Marx 1999a; Marx 1999b). The other eight studies specified exclusion of those unfit for compression. The subjects in Annane 2004 had 2 months of prior therapy with antibiotics, wound irrigation and surgery, but no details were given in the other studies. Marx 1985 specified a minimum prior radiation dose of 6000 cGy at least 6 months prior to enrolment. Teguh 2009 specified treatment of head and neck tumours with a dose of 46 to 70 Gy and Schoen 2007 included patients suitable for dental implant placement in patients previously irradiated in the relevant area. All the patients in Gothard 2010 had ipsilateral arm swelling of more than 15% compared to the unaffected side.

Blinding

Three studies utilised a sham therapy in order to mask subjects and outcome assessors to HBOT (Annane 2004; Clarke 2008; Pritchard 2001), while no sham was employed in the remaining seven studies. Only Clarke 2008 formally tested the success of the blinding strategy.

Patients lost to follow-up

Eight studies did not report any losses to follow-up or violation of the study protocol (Annane 2004; Gothard 2010; Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Pritchard 2001; Teguh 2009). Clarke 2008 did not include 19 control subjects and 11 HBOT group subjects in the analysis because they did not complete the therapy protocol, and there was one further subject lost to follow-up at the end of treatment. Schoen 2007 reported that six patients were lost to final follow-up at 1 year. Sensitivity analysis using best- and worse-case scenarios were performed where this study contributed data to the analysis.

Intention-to-treat analysis

Only Pritchard 2001 specifically detailed an ITT analysis (two subjects in the HBOT group did not complete therapy, but were included in analysis). Seven of the remaining nine studies reported full follow-up and did not report any protocol violation (see above).

Effects of interventions

See: **Summary of findings for the main comparison** Hyperbaric oxygen therapy for late radiation tissue injury

Combined anatomical areas

Primary outcomes

(1) Death

Annane 2004 reported two deaths in each group at 1 year, two from cancer regrowth and two from other causes not related to their ORN (the RR of dying following HBOT is estimated at 0.84; 95% CI 0.13 to 5.61). Clarke 2008 reported five deaths at 1 year, but this cross-over study did not identify the original treatment allocation, while Schoen 2007 reported that two enrolled patients died during the study, but their group allocation was not specified. Therefore these latter two trials did not contribute to this analysis.

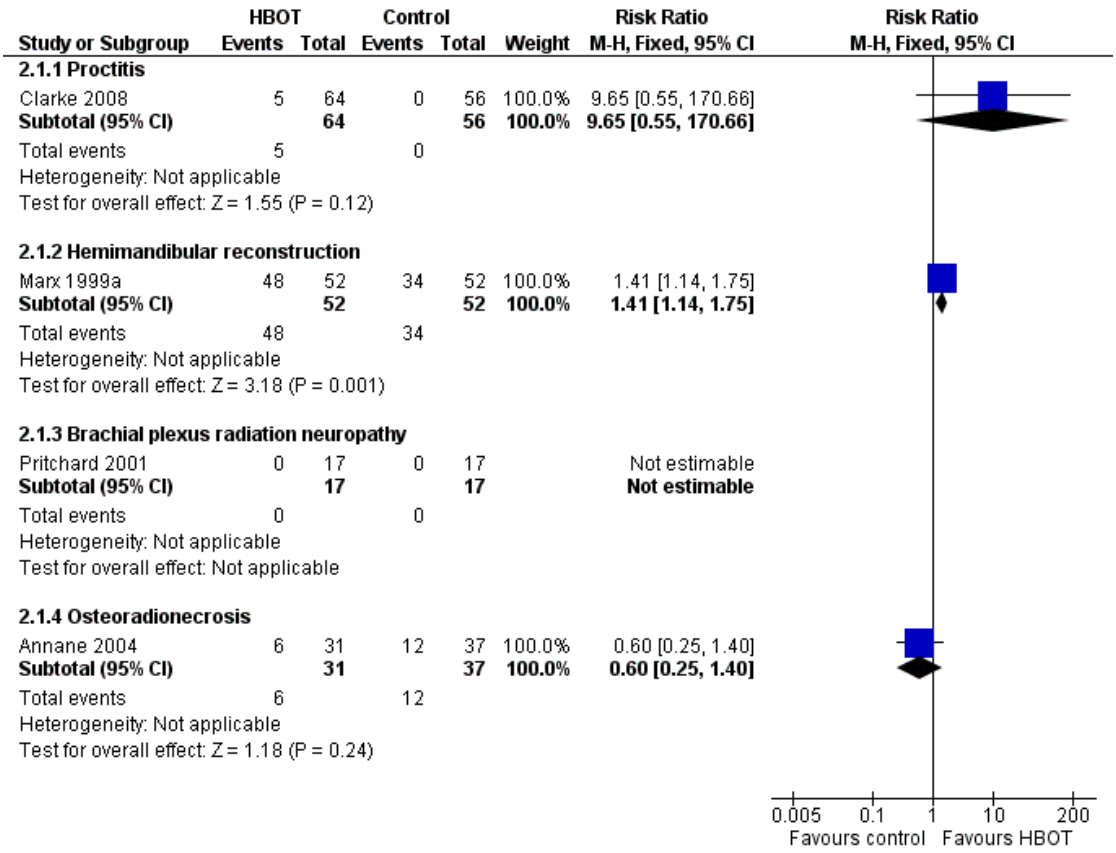
(2) Complete resolution of tissue damage or necrosis

(a) Complete resolution of clinical problem at or before 3 months (Analysis 2.1)

Four trials reported this outcome (Annane 2004; Clarke 2008; Marx 1999a; Pritchard 2001), involving 325 participants, with 163 randomised to HBOT and 162 to control. Overall, 59 (36%) of participants in the HBOT group achieved resolution versus 46 (28%) in the control group. Analysis for heterogeneity suggested the high proportion of variability between trials was not due to sampling variability (I^2 = 82%), and we have not quantified an overall estimate of effect. Pritchard 2001 did not report any participants with resolution in either group, so could not contribute to the analysis.

There was a significantly improved probability of resolution with the administration of HBOT for patients requiring hemimandibulectomy (RR 1.4, 95% CI 1.1 to 1.8, P = 0.001, Marx 1999a) and a non-significant improvement for radiation proctitis (RR 9.7; 95% CI 0.6, 170.1, P = 0.12, Clarke 2008). However, the result for proctitis was highly sensitive to the allocation of dropouts (best case: RR 33.0; 95% CI 2.0 to 540.2, P = 0.01, (Analysis 2.2); worst case: RR 0.31; 95% CI 0.12 to 0.81, P = 0.02 (Analysis 2.3)). For participants requiring hemimandibulectomy, 48 (92%) achieved resolution following HBOT versus 34 (65%) in the control group, and the NNTB to achieve one extra case of resolution is 4, (95% CI 2 to 8). On the other hand, there was no improvement in the chance of resolution for patients with ORN of the mandible in the Annane 2004 study (RR 0.6, 95% CI 0.25 to 1.4, P = 0.24). See Figure 3.

Figure 3. Forest plot of comparison: 2 Complete resolution of problem, outcome: 2.1 Complete resolution of clinical problem at end of therapy to 3 months.



(b) Development of ORN following dental implants.

Schoen 2007 reported on this outcome in 26 previously irradiated patients deemed suitable for the placement of dental implants. One patient in the HBOT group developed ORN versus no patients in the control group. The risk of ORN was not significantly different (RR 3.0, 95% CI 0.13 to 67.5, P = 0.49 (Analysis 2.4)).

(3) Complete resolution or significant improvement of tissue damage or necrosis

Clarke 2008 reported this combined outcome immediately after completion of therapy. This trial reported on 119 participants, with 64 randomised to HBOT and 56 to control. 29 (46%) of participants in the HBOT group achieved this outcome versus 15 (27%) in the control group. This difference was statistically significant (RR for improvement in HBOT 1.72, 95% CI 1.0 to 2.9, P = 0.04 (Analysis 3.1)), but is sensitive to the allocation of dropouts and those missing (best case: RR 2.73, 95% CI 1.66 to 4.49, P < 0.0001 (Analysis 3.2); worst case: RR 0.66; 95% CI 0.47 to 0.93, P = 0.04 (Analysis 3.3)). This analysis suggests we would have to treat five patients with HBOT in order to achieve one extra favourable outcome (NNTB 5; 95% CI 3 to 23).

(4) LENT-SOMA scores

(a) Improvement in LENT-SOMA score at completion of therapy

Only one trial reported this outcome (Clarke 2008) involving 150 subjects, with 75 randomised to both HBOT and control. The mean improvement in LENT-SOMA score was greater in the HBOT group (5.0 with HBOT versus 2.6 with control), and this difference was statistically significant (MD 2.4; 95% CI 0.89 to 3.9, P = 0.002).

Secondary outcomes

(5) Pain scores

(a) Change in pain score (0 to 100 scale) from baseline to 6 months after treatment (comparison 05, outcome 01)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients with 17 randomised to both HBOT and control. Pain scores increased over this time period in both groups, but more so with HBOT (5.3 points with HBOT versus 1.2 points with control). Standard deviations were not reported around these means, precluding further analysis.
(b) Change in pain score (0 to 100 scale) from baseline to 12 months after treatment (comparison 05, outcome 02)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients with 17 randomised to both HBOT and control. Pain scores were reduced in both groups, but more so in the controls (-5.0 points with HBOT versus -0.7 with control). Standard deviations were not reported around these means, precluding further analysis.

(6) Swelling

(a) Resolution of lymphoedema in arm at 6 months (Analysis 6.1)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients with 17 randomised to both HBOT and control. Two subjects (12%) in the HBOT group achieved resolution, while none in the control group did so. This difference in favour of HBOT was not statistically significant (RR of resolution with HBOT 5.0; 95% CI 0.3 to 97.0, P = 0.29).
(b) Reduction in lymphoedema at 12 months (Analysis 6.2)
Only one trial reported this outcome (Gothard 2010), involving 58 patients, with 30 randomised to HBOT and 16 to control. There was no significantly greater reduction in the relative volume of the affected arm after treatment with HBOT (2.6% reduction in volume) compared to the control group (0.3% reduction) (MD in reduction +2.6%; 95% CI -13.5 to +18.7, P = 0.75).
These authors also reported the proportion of patients achieving a > 8% reduction in volume of the arm; 9/30 (30%) did so in the HBOT group versus 3/16 (19%) in the control group (RR 1.86; 95% CI 0.42 to 8.15, P = 0.41 (Analysis 6.3)).

(7) QoL or functional scores

(a) Short Form (SF)-36 score for general health at 12 months
Only one trial reported this outcome (Pritchard 2001) involving 34 patients with 17 randomised to both HBOT and control. The mean score for general health self-rating was lower in the HBOT group (58.8 with HBOT versus 61.1 with control), but this was not significant (WMD -2.3; 95% CI -19.0 to +14.4, P = 0.79).

(b) SF-36 score for physical functioning at 12 months
Only one trial reported this outcome (Pritchard 2001) involving 34 patients with 17 randomised to both HBOT and control. The mean score for self-rating of physical functioning was lower in the HBOT group (53.5 with HBOT versus 57.5 with control), but this was not significant (WMD -4.0; 95% CI -19.4 to +11.4, P = 0.61). Gothard 2010 also reported no significant differences between the allocated groups at 12 months, but did not report the data.
(c) Bowel bother subscale at completion of therapy
Only one trial reported this outcome (Clarke 2008) involving 150 patients with 75 randomised to each of HBOT and sham therapy. This trial reported a statistically significant mean improvement of 14.1% (P = 0.0007) in this subscale following HBOT compared to a non-significant mean improvement of 5.8% (P = 0.15) in the sham group.
(d) Lymphoedema specific questionnaire at 12 months
Only one trial reported this outcome (Gothard 2010), involving 58 patients, with 38 randomised to HBOT and 20 to control. This is a self-assessment subscale of functional effect and is rated from 0 (no effect) to 100 (maximum effect). There was no significant difference between the groups at 12 months' estimation (HBOT median score 37.5; interquartile range (IQR) 20.8 to 52.1; control 45.8; IQR 13.0 to 62.5, P value not given).
(e) QoL scores in head and neck cancers
Teguh 2009 reported QoL in the form of Items relating to xerostomia and dysphagia from the European Organisation for Research and Treatment of Cancer (EORTC), Head and Neck cancer module (H&N35) at a number of time points. They also determined a visual analogue scale (VAS) for 'dry mouth' and 'pain in the mouth'. The results at 12 months are given here, but the P values are calculated from "regression analysis based on maximum likelihood estimation and incorporating the longitudinal character of the data." At 12 months, the H&N35 sticky saliva score (0 = nil, 100 = maximum) was 25 for those who received HBOT versus 62 for controls (P = 0.01), the H&N35 scores for dry mouth (same scale) were 28 for those receiving HBOT versus 92 for controls (P = 0.009), the H&N35 scores for difficulty swallowing (same scale) were 7 for those receiving HBOT versus 40 for controls (P = 0.011); the VAS for 'dry mouth' (0 = nil, 10 = maximum) were 3.4 for those receiving HBOT versus 7.2 for controls (P value not given) and the VAS for 'pain in the mouth' (same scale) were 0.8 for those receiving HBOT versus 6.6 for the controls (P < 0.0001).
(f) QoL scores following dental implants into an irradiated area
Schoen 2007 reported on both global QoL estimates using the 30 question 'core questionnaire' of the EORTC H&N35 (0 to 100 scale, higher scores indicate better QoL) and the individual elements of that questionnaire. The global score was 66.7 ± 13.6 in the HBOT group versus 84.3 ± 19.7 in the control group and an isolated analysis suggests a better outcome in the absence of HBOT (MD 17.6 points; 95% CI 2.8 points to 32.4 points, P = 0.02). The authors analysed the changes from baseline in each and found no significant differences between groups because entry scores were lower in the HBOT group.

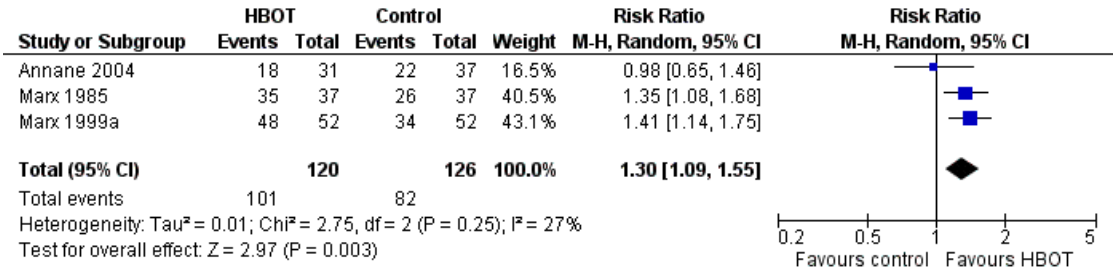
(8) ORN

Primary outcomes

(a) Achievement of complete mucosal cover

Three trials reported this outcome (Annane 2004; Marx 1985; Marx 1999a), involving 246 subjects, with 120 randomised to HBOT and 126 to control. A total of 101 (84%) subjects in the HBOT group achieved mucosal cover versus 82 (65%) in the control group. Heterogeneity was moderate (I^2 = 27%), and explained by the addition of data from Annane 2004 (I^2 = 0% without Annane 2004). Overall, there was a significantly improved probability of attaining mucosal cover with the administration of HBOT (RR 1.3; 95% CI 1.1 to 1.6, P = 0.003 (Analysis 8.1)). The NNTB to achieve one further case with mucosal cover with the application of HBOT was 5 (95% CI 3 to 12). See Figure 4.

Figure 4. Forest plot of comparison: 8 Osteoradionecrosis, outcome: 8.1 Complete mucosal cover.



(b) Establishment of bony continuity

Only one trial contributed results to this outcome (Marx 1999a) involving 104 subjects, 52 randomised to both HBOT and control. Forty eight (92%) subjects in the HBOT group achieved continuity, versus 60 (65%) in the control group. There was a significantly improved probability of attaining bony continuity with the administration of HBOT (RR 1.4; 95% CI 1.1 to 1.8, P = 0.001 (Analysis 8.2)). The NNTB to achieve one further case with bony continuity with the application of HBOT was 4 (95% CI 2 to 8).

(c) Resolution of sinus tract

No study reported data on this outcome.

(d) Healing of tooth sockets following extraction in irradiated field at 6 months

Only one trial contributed results to this outcome (Marx 1985) involving 74 subjects, 37 randomised to both HBOT and control. Thirty five (95%) subjects in the HBOT group achieved healing of all sockets versus 26 (70%) in the control group. There was a significantly improved probability of healing with the administration of HBOT (RR 1.4; 95% CI 1.1 to 1.7, P = 0.009 (Analysis 8.4)). The NNTB with HBOT to achieve one further case with all tooth sockets healed was 4 (95% CI 2 to 13).

Secondary outcomes

(e) Improvement in X-ray appearance

Schoen 2007 reported the radiological evidence of bone loss at 12 months from implant. The loss was 0.6 ± 0.6 mm for the HBOT group versus 0.7 ± 0.7 mm for control subjects and there was no statistically significant difference between groups (MD 0.1 mm less with HBOT, 95% CI 0.67 in favour of HBOT to 0.47 in favour of control, P = 0.73 (Analysis 8.5)).

(9) Head and neck tissues

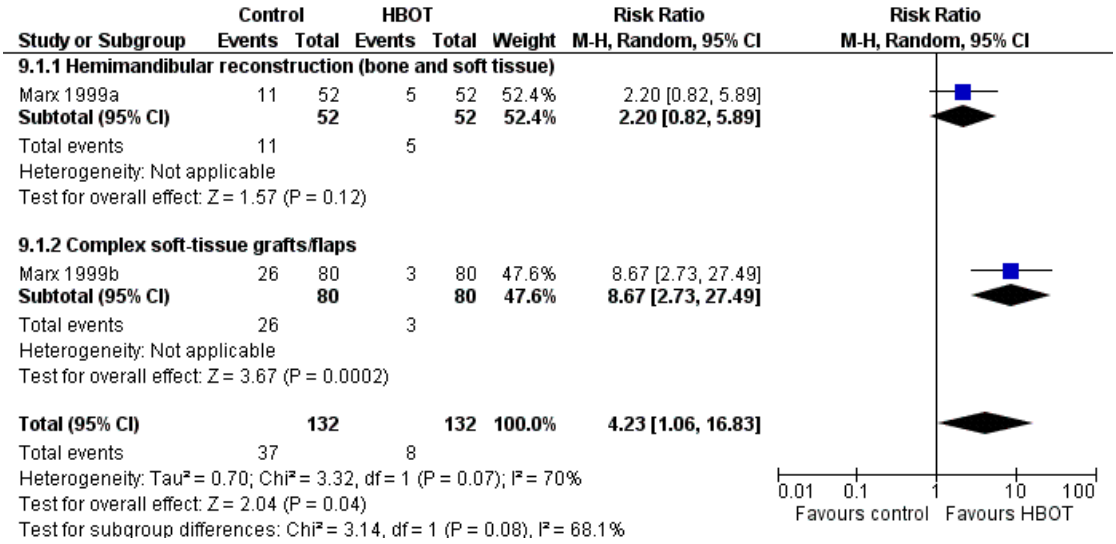
Primary outcomes

(a) Wound dehiscence

Two trials reported this outcome (Marx 1999a; Marx 1999b), involving 368 subjects, with 184 randomised to both HBOT and control groups. Overall, eight (6%) people in the HBOT group suffered wound breakdown versus 37 (28%) in the control group. Analysis for heterogeneity suggested a high proportion of variability between trials was not due to sampling variability (I^2 = 70%), and so this comparison was made using a random-effects model. There was a significantly improved chance of wound breakdown with control (RR 4.2; 95% CI 1.1 to 16.8, P = 0.04 (Analysis 9.1)). Stratification by tissue type involved confirmed the direc-

tion of effect was the same for both studies, but it remained significant only for soft tissue flaps and grafts (RR following hemimandibulectomy (Marx 1999a) 2.2; 95% CI 0.8 to 5.9, P = 0.12; RR following soft tissue flap or graft (Marx 1999b) 8.7; 95% CI 2.7 to 27.5, P = 0.0002). The number needed to treat to benefit with HBOT to avoid one wound dehiscence overall was 5 (95% CI 1 to 59), and for soft tissue repairs alone was 4 (95% CI 3 to 6). See Figure 5.

Figure 5. Forest plot of comparison: 11 Head and Neck, outcome: 11.1 Wound dehiscence.



(b) Loss of dental implant (comparison 09, outcome 02)

Schoen 2007 reported on the number of patients with lost implants following implant into an irradiated mandible in 26 patients. Eight implants were lost in the hyperbaric patients (5 individuals) versus 3 implants (2 individuals) in the control group. The risk of losing an implant was 2.5 greater following HBOT, but this was not statistically significant (RR 2.50; 95% CI 0.59 to 10.64, P = 0.22 (Analysis 9.2)).

(b) Surgical removal of the larynx

No study reported data on this outcome.

(c) Major bleeding

No study reported data on this outcome.

Secondary outcomes

(d) Speed of wound healing

No study reported data on this outcome.

(e) Improvements in tissue quality

No study reported data on this outcome.

(f) Reversal of tracheostomy

No study reported data on this outcome.

(10) Urinary bladder

No study reported data on outcomes for this tissue.

(11) Chest wall

No study reported data on outcomes for this tissue.

(12) Bowel

No study reported data on outcomes for this tissue.

(13) Neurological tissue

Primary outcomes

(a) Objective motor function

No study reported data on this outcome.

(b) Visual acuity

No study reported data on this outcome.

Secondary outcomes

(c) Warm sensory threshold at 1 week after therapy

Only one trial reported this outcome (Pritchard 2001) involving 34 patients with 17 randomised to both HBOT and control. The mean threshold temperature for reporting a warm sensation at 1 week after therapy (compared to pretreatment baseline) was reduced in the HBOT group, but not in the control group (-0.1 degree with HBOT versus 1 degree with control). This difference was not statistically significant (MD -1.1 degrees; 95% CI -1.9 degrees to 4.1 degrees, P = 0.47 (Analysis 13.1)).

(d) Warm sensory threshold at 1 year after therapy

Only one trial reported this outcome (Pritchard 2001) involving 34 patients with 17 randomised to both HBOT and control. The mean threshold for reporting a warm sensation was increased in both groups, but less so in controls (0.5 degrees with HBOT versus 1.4 degrees with control). This difference was not statistically significant (MD -0.9 degrees; 95% CI -4.0 degrees to 2.2 degrees, P = 0.58 (Analysis 13.2)).

(e) Functional ability scores and ADL

No study reported data on this outcome.

(f) Net number of neuropsychological tests (maximum 25 tests) improved at 3 months

Only one trial reported this outcome (Hulshof 2002) involving seven patients with four randomised to HBOT and three to control. The mean net number of improved tests was greater in the HBOT group (3.3 with HBOT versus 1.3 with control), but this was not significant (MD 2; 95% CI -1.6 to 5.0, P = 0.28 (Analysis 13.3)).

(g) Net number of neuropsychological tests (maximum 25 tests) improved at 6 months

Only one trial reported this outcome (Hulshof 2002) involving seven patients with four randomised to HBOT and three to control. The mean net number of improved tests was greater in the HBOT group (3 with HBOT versus 2 with control), but this was not significant(weighted mean difference (WMD) 1.1; 95% CI -3.6 to 5.6, P = 0.67 (Analysis 13.4)).

(14) Adverse events

No study reported comparative data on these outcomes. Clarke 2008 and Gothard 2010 gave overall figures for adverse events in all patients completing treatment. Nineteen (16%) patients complained of ear pain Clarke 2008, while 2 (5%) were offered tympanostomy tubes in Gothard 2010. Four (3%) and three (8%) complained of transient myopia in these two studies respectively, and two (1.7%) of confinement anxiety in Clarke 2008. Schoen 2007 and Teguh 2009 reported that the treatment was 'well tolerated' in their patients.

DISCUSSION

This review has identified 11 trials investigating the use of HBOT for tissue suffering from LRTI, and we believe these represent all randomised human trials in this area, both published and unpublished, at the time of searching the databases. This review was updated in January 2012 and three new studies included. These studies enrolled patients with radiation injury to the head and neck (Schoen 2007; Teguh 2009) and the axilla (Gothard 2010). While all have contributed to this review, the final conclusions have not been substantially altered.

In general, these trials suggest a benefit from HBOT for non-neurological radiation tissue injury. The scant available evidence for neurological tissue is not encouraging. Any benefit from HBOT for the treatment of ORN is not reflected in the results of Annane 2004. There are several reasons why this might be so. First, this trial did not test the usual treatment regimen employed for the management of ORN and may not therefore be directly comparable with the other trials in this review. Case series data from the 1980s suggest that HBOT in isolation is not associated with a high resolution rate for established ORN and most centres now employ a combination of operative therapy, antibiotics and HBOT, as described by Marx (the Wilford Hall Protocol) (Marx 1983). One automatic definition of poor outcome for Annane 2004 was the requirement for operative therapy in cases presenting with less-extensive disease, whether or not full recovery was eventually achieved. However, these cases would be reported as successes in the other included trials. Second, 66 of the 134 (49%) patients presenting with ORN during the study period were ineligible for inclusion, making generalisation of the findings of this trial to more advanced cases of ORN (such as those presented in Marx 1999a and Marx 1999b) problematic. The first author has subsequently confirmed that "..one cannot use the findings of our study to decide the optimal treatment of severe forms of mandibular necrosis" (personal communication, April 2008). Third, of the 50 patients in this trial that did not have a good outcome at 1 year, 34 were described as suffering previous treatment failure, which may have biased the result against superiority for either group. Finally, this trial was stopped (according to pre-defined rules) with only 68 patients included and before a statistically significant result had been achieved. Any of these factors may have influenced the outcome of this trial. It is also possible that advances in care have taken place over time, such that HBOT no longer carries a therapeutic benefit.

The single small trial including irradiated patients who were suitable for the placement of dental implants (Schoen 2007) did not suggest HBOT was of any benefit either in the chance of successful osseointegration or the avoidance of ORN.

The full report of Clarke 2008 generally confirms the results reported in abstract at an interim stage. The magnitude of effect for HBOT is reduced, but the direction remains in favour of HBOT. This trial did not present results for 31 of the 150 patients enrolled and sensitivity analysis for best and worst case outcomes in these missing patients has somewhat reduced our confidence in the effect of HBOT in radiation proctitis.

We found some evidence that HBOT improves the probability of healing in radiation proctitis and following hemimandibulectomy and reconstruction of the mandible, improves the probability of achieving mucosal coverage and the restoration of bony continuity with ORN, prevents the development of ORN following tooth extraction from a radiation field and reduces the risk of wound dehiscence following grafts and flaps in the head and neck. Although there was some trend towards secondary favourable outcomes in neurological tissue, there was no evidence of benefit in important clinical outcomes with established radiation brachial plexus lesions or cerebral tissue injury. There were no data reported from any randomised trials involving the use of HBOT to treat other manifestations of radiation tissue damage.

Several trials reported different measures of QoL and functional outcome following HBOT for radiation injury in the head and neck (Schoen 2007; Teguh 2009) bowel (Clarke 2008) and axilla (Gothard 2010; Pritchard 2001). No pooling was appropriate for these outcomes. In general, these trials presented positive improvements with the head and neck and bowel, but not the neurological injury or lymphoedema associated with axillary radiation injury. One factor that may have influenced this was the well-established nature of the axillary injury in Pritchard 2001 and Gothard 2010 (88% had a time from radiotherapy to HBOT of 10 years or more in Pritchard 2001, mean time from radiotherapy to HBOT more than 11 years in Gothard 2010).

Only 11 trials with 669 participants were available for evaluation using our planned comparisons, and meta-analysis was not appropriate or possible for most of these. Many of the trials enrolled modest numbers of patients, particularly the trial investigating cerebral radiation injury, where only seven subjects were reported (Hulshof 2002). Other problems for this review were the poor methodological quality of some of these trials (particularly Marx 1999a; Marx 1999b), variability in entry criteria and the nature and timing of outcomes, and poor reporting of both outcomes and methodology. In particular, there is a possibility of bias in the combined tissue outcomes due to different anatomical locations and extent of tissue damage on entry to these trials, as well as from non-blinded management decisions in three of the trials (Marx 1985; Marx 1999a; Marx 1999b). Further, it is not clear when the subjects for Marx 1999a and Marx 1999b were recruited - these trials may represent work from some years earlier.

These trials were published over a 25-year period up to 2010, and from a wide geographical area. We had planned to perform subgroup analyses with respect to anatomical location, dose of oxygen received (pressure, time and length of treatment course), nature of the comparative treatment modalities and the severity of injury. However, the paucity of eligible trials and poor reporting of some trials suggested that, except for anatomical location, these analyses would not be informative. The oxygen dose used was reasonably standard over most trials. Patient inclusion criteria were not standard, and poorly reported in some trials. Specific comparator therapies were generally not employed.

Four trials reported on complete resolution of the clinical problem (Annane 2004; Clarke 2008; Marx 1999a; Pritchard 2001). Results varied widely and could not be pooled. Clarke 2008 and Marx 1999a reported significant improvement in the chance of healing radiation proctitis (RR 1.72, P = 0.04, NNTB 5), and following hemimandibulectomy and reconstruction (RR 1.4, P = 0.001, NNTB 4) respectively. Pritchard 2001, in contrast, reported no such resolution in any subject treated for established radiation brachial plexopathy. This difference in outcome could reflect the unresponsiveness of neurological tissue in general (an assertion supported by a similar lack of response for brain radiation injury in Hulshof 2002, or the relatively long-standing nature of the injuries enrolled in that trial (mean period from radiotherapy to HBOT was 11 years)).

Pooling of data for clinical outcomes of interest could only be performed with respect to the achievement of complete mucosal cover in mandibular ORN and the risk of wound dehiscence. These analyses suggested some benefit from HBOT administration (RR for complete mucosal cover with HBOT 1.3; 95% CI 1.1 to 1.6, NNTB 5; 95% CI 2 to 12; RR of dehiscence with control group 4.2; 95% CI 1.1 to 16.8, NNTB 5; 95% CI 3 to 8). These results are subject to a high proportion of variability being due to differences between trials rather than to sampling variability, and should be interpreted with great caution. However, these possible treatment effects are of great clinical importance and deserve further investigation.

The incidence of adverse effects was not systematically reported by the studies included in this review. There are a number of minor complications that may occur commonly. Visual disturbance, usually reduction in visual acuity secondary to conformational changes in the lens, is very commonly reported - perhaps as many as 50% of those having a course of 30 treatments (Khan 2003). While the great majority of patients recover spontaneously over a period of days to weeks, a small proportion of patients continue to require correction to restore sight to pretreatment levels. Only four of 63 patients receiving HBOT in Clarke 2008 reported a reduction in visual acuity. All were temporary. The second most common adverse effect associated with HBOT is middle-ear barotrauma. Barotrauma can affect any air-filled cavity in the body (including the middle ear, lungs and respiratory sinuses) and occurs as a direct result of compression. Ear barotrauma is by far the most common as the middle ear air space is small, largely surrounded by bone and the sensitive tympanic membrane, and usually requires active effort by the patient in order to inflate the middle ear through the Eustachian tube on each side. Barotrauma is thus not a consequence of HBOT directly, but rather of the physical conditions required to administer it. Most episodes of barotrauma are mild, easily treated or recover spontaneously and do not require the therapy to be abandoned.

While we have made every effort to locate further unpublished data, it remains possible that this review is subject to a positive publication bias, with generally favourable trials more likely to achieve reporting. With regard to long-term outcomes following HBOT and any effect on the QoL for these patients, we have located few relevant data.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence that HBOT improves outcome in LRTI affecting bone and soft tissues of the head and neck, for radiation proctitis and to prevent the development of ORN following tooth extraction in an irradiated field. There was no such evidence of any important clinical effect on neurological tissues, either peripheral or central. Thus, the application of HBOT to selected patients and tissues may be justified. While the small number of studies, the modest numbers of patients and the methodological and reporting inadequacies of some of the primary studies included in this review demand a cautious interpretation, the pathology of radiation injury suggests that other tissues are also likely to respond (e.g. bladder). Further research is required to establish the optimum patient selection and timing of any such therapy. An economic evaluation should also be undertaken.

Implications for research

There is a strong case for further large randomised trials of high methodological rigour in order to define the true extent of benefit from the administration of HBOT for patients with LRTI. Specifically, more information is required on the subset of disease severity and tissue type affected that is most likely to benefit from this therapy, the time for which we can expect any benefits to persist and the oxygen dose most appropriate. Any future trials would need to consider in particular:

- appropriate sample sizes with power to detect expected differences generated by this review
- careful definition and selection of target patients
- appropriate oxygen dose per treatment session (pressure and time)
- appropriate supportive therapy to which HBOT would be an adjunct
- use of an effective sham therapy
- effective and explicit blinding of outcome assessors
- appropriate outcome measures including all those listed in this review
- careful elucidation of any adverse effects
- the cost-utility of the therapy

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Annane 2004 ***{published data only (unpublished sought but not used)}***
Annane D, Depondt J, Aubert P, Villart M, Gehanno P, Gajdos P, et al.Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 Study Group. *Journal of Clinical Oncology* 2004;**22**(24):4893–900.

Clarke 2008 ***{published data only (unpublished sought but not used)}***
Clarke D, Tenorio C, Dominguez L, Toklu A, Hussey J. Treatment of radiation necrosis with hyperbaric oxygen: a randomized double-blind placebo controlled trial. *Undersea and Hyperbaric Medicine* 2004;**31**(Suppl).
Clarke RE, Catalina Tenorio LM, Hussey JR, Toklu AS, Cone DL, Hinojosa JG, et al.Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomised and controlled double-blind crossover trial with long-term follow-up. *International Journal of Radiation Oncology, Biology, Physics* 2008;**72**:134–43.

Gothard 2010 ***{published data only}***
Gothard L, Haviland J, Bryson P, Laden G, Glover M, Harrison S, et al.Randomised phase II trial of hyperbaric oxygen therapy in patients with chronic arm lymphoedema after radiotherapy for cancer. *Radiotherapy and Oncology* 2010;**97**(1):101–7.

Hulshof 2002 ***{published data only}***
* Hulshof M, Stark N, Van der Kleij A, Sminia P, Smeding H, Gonzales D. Hyperbaric oxygen therapy for cognitive disorders after irradiation of the brain. *Strahlentherapie und Onkologie* 2002;**178**(4):192–8. [MEDLINE: 2002140155]

Marx 1985 ***{published data only}***
* Marx R, Johnson R, Kline S. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *Journal of the American*

Dental Association 1985;**111**(1):49–54. [MEDLINE: 3897335]

Marx 1999a *{published data only}*

* Marx R. Bony reconstruction of the jaw. In: Kindwall EP, Whelan HT editor(s). *Hyperbaric Medicine Practice*. 2nd Edition. Flagstaff, Az: Best Publishing, 1999:460–3. [MEDLINE: 0-941332-78-0]

Marx 1999b *{published data only}*

* Marx RE. Soft tissue flaps. In: Kindwall EP, Whelan HT editor(s). *Hyperbaric Medicine Practice*. 2nd Edition. Flagstaff, Az: Best Publishing, 1999:464–8. [: 0–941332–78–0]

Pritchard 2001 *{published data only}*

* Pritchard J, Anand P, Broome J, Davis C, Gothard L, Hall E, et al.Double-blind randomized phase II study of hyperbaric oxygen in patients with radiation-induced brachial plexopathy. *Radiotherapy and Oncology* 2001;**58**(3): 279–86. [MEDLINE: 2001084162]
Yarnold J. Double-blind randomised phase II study of hyperbaric oxygen in patients with radiation-induced brachial plexopathy. *Radiotherapy and Oncology* 2005;**77**(3): 327.

Schoen 2007 *{published data only}*

Schoen PJAU, Raghoebar GMAU, Bouma JAU, Reintsema HAU, Vissink AAU, Sterk WAU, et al.Rehabilitation of oral function in head and neck cancer patients after radiotherapy with implant-retained dentures: effects of hyperbaric oxygen therapy. *Oral Oncology* 2007;**43**(4):379–88.

Sidik 2007 *{published data only}*

Sidik S, Hardjodisastro D, Setiabudy R, Gondowiarjo S. Does hyperbaric oxygen administration decrease side effects and improve quality of life after pelvic irradiation?. *Acta Medica Indonesiana* 2007;**39**(4):169–73.

Teguh 2009 *{published data only}*

Teguh DN, Levendag PC, Noever I, Voet P, van der Est H, van Rooij P, et al. Early hyperbaric oxygen therapy for reducing radiotherapy side effects: early results of a randomized trial in oropharyngeal and nasopharyngeal cancer. *International Journal of Radiation Oncology, Biology, Physics* 2009;**75**(3):711–6.

References to studies excluded from this review

Carl 2001 *{published data only}*

* Carl U, Feldmeier J, Schmitt G, Hartmann K. Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery. *International Journal of Radiation Oncology Biology and Physics* 2001;**49** (4):1029–31. [MEDLINE: 11240244]

Coulthard 2002 *{published data only}*

Couthard P, Esposito M, Worthington H, Jokstad A. Interventions for replacing missing teeth: hyperbaric oxygen therapy for irradiated patients who require dental implants. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD003603]

Denton 2002 *{published data only}*

Denton A, Forbes A, Andreyev J, Maher E. Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. *Cochrane Database of Systematic Reviews* 2002, Issue 1. [DOI: 10.1002/14651858.CD003455]

Gal 2003 *{published data only}*

* Gal T, Yueh B, Futran N. Influence of prior hyperbaric oxygen therapy in complications following microvascular reconstruction for advanced osteoradionecrosis. *Archives of Otolaryngology - Head & Neck Surgery* 2003;**129**(1):72–6. [MEDLINE: 2003027602]

Granstrom 1999 *{published data only}*

* Granstrom G, Tjellstrom A, Branemark P-I. Osseointegrated implants in irradiated bone: a case-controlled study using adjunctive hyperbaric oxygen therapy. *Journal of Oral and Maxillofacial Surgery* 1999;**57**: 493–9. [: 0278–2391]

Maier 2000 *{published data only}*

* Maier A, Gaggl A, Klemen H, Santler G, Anegg U, Fell B, et al.Review of severe osteoradionecrosis treated by surgery alone or surgery with postoperative hyperbaric oxygenation. *British Journal of Oral and Maxillofacial Surgery* 2000;**38**(3): 173–6. [MEDLINE: 10864721]

Niimi 1997 *{published data only}*

* Niimi A, Fujimoto T, Nosaka Y, Ueda M. A Japanese multicenter study of osseointegrated implants placed in irradiated tissues: a preliminary report. *International Journal of Oral and Maxillofacial Implants* 1997;**12**(2):259–64. [MEDLINE: 9109278]

Tobey 1979 *{published data only}*

* Tobey R, Kelly J. Osteoradionecrosis of the jaws. *Otolaryngology Clinics of North America* 1979;**12**(1):183–6. [MEDLINE: 375158]

References to studies awaiting assessment

DAHANCA 2011 *{unpublished data only}*

Forner L. DAHANCA 21: Hyperbaric Oxygen Treatment of Mandibular Osteoradionecrosis. www.dahanca.dk/home Still in planning.

HOPON 2011 *{published data only}*

Bickerstaff M. HOPON: Hyperbaric Oxygen for the Prevention of Osteoradionecrosis. www.lctu.org.uk Still recruiting.

References to ongoing studies

Clarke 2004b *{published and unpublished data}*

Hyperbaric Oxygen for Radiation Tissue Injury Study (HORTIS). Ongoing study 1999.

Additional references

Altman 2001

Altman D, Chalmers I, Egger M, Davey Smith G. In: Egger M, Davey Smith G, Altman D editor(s). *Systematic*

reviews in health care. Meta-analysis in context. 2nd Edition. London: BMJ Books, 2001:333.

Bennett 2011
Bennett M, Connor D. The database of randomised controlled trials in hyperbaric medicine. http://www.hboevidence.com/ (accessed 18 March 2012).

Davis 1988
Davis JC, Buckley CJ, Barr P. Compromised soft tissue wounds: correction of wound hypoxia. In: Davis JC, Hunt TK editor(s). *Problem Wounds. The Role of Oxygen*. New York: Elsevier, 1988:143–52.

Feldmeier 1995
Feldmeier JJ, Heimbach RD, Davolt DA, Court WS, Stegmann BJ, Sheffield PJ. Hyperbaric oxygen as an adjunctive treatment for delayed radiation injury of the chest wall: a retrospective review of twenty-three cases. *Undersea and Hyperbaric Medicine* 1995;**22**(4):383–93. [MEDLINE: 8574126]

Feldmeier 1998
Feldmeier JJ, Davolt DA, Court WS, Onoda JM, Alecu R. Histologic morphometry confirms a prophylactic effect for hyperbaric oxygen in the prevention of delayed radiation enteropathy. *Undersea and Hyperbaric Medicine* 1998;**25**(2): 93–7. [MEDLINE: 9670434]

Feldmeier 2002
Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. *Undersea and Hyperbaric Medicine* 2002;**29**(1):4–30. [MEDLINE: 12507182]

Feldmeier 2003
Feldmeier J, Carl U, Hartmann K, Sminia P. Hyperbaric oxygen: does it promote growth or recurrence of malignancy?. *Undersea and Hyperbaric Medicine* 2003;**30** (1):1–18. [MEDLINE: 12841604]

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hills 1999
Hills BA. A role for oxygen-induced osmosis in hyperbaric oxygen therapy. *Medical Hypotheses* 1999;**52**:259–63.

Jain 2009
Jain KK. *Textbook of Hyperbaric Medicine*. New York: Hogrefe & Huber Publishers, 2009.

Jemal 2002
Jemal A, Thomas A, Murray T, Thun M. Cancer statistics. *CA: A Cancer Journal for Clinicians* 2002;**52**:23–47.

Khan 2003
Khan B, Evans AW, Easterbrook M. Refractive changes in patients undergoing hyperbaric oxygen therapy: a prospective study. *Undersea and Hyperbaric Medicine* 2003; **24 (Suppl)**:9.

Kindwall 2008
Kindwall EP, Whelan HT. Hyperbaric Medicine Practice. *Hyperbaric Medical Practice*. 3rd Edition. Flagstaff Az: Best Publishing Company, 2008.

Mainous 1975
Mainous EG, Hart GB. Osteoradionecrosis of the mandible. Treatment with hyperbaric oxygen. *Archives of Otolaryngology* 1975;**101**(3):173–7. [MEDLINE: 804303]

Mandell 1974
Mandell GL. Bactericidal activity of aerobic and anaerobic polymorphonuclear neutrophils. *Infection and Immunology* 1974;**9**:337–41.

Marx 1983
Marx RE. A new concept in the treatment of osteoradionecrosis. *Journal of Oral and Maxillofacial Surgery* 1983;**41**:351–7.

Marx 1988
Marx RE, Johnson RP. Problem wounds in oral and maxillo-facial surgery: the role of hyperbaric oxygen. In: Davis JC, Hunt TK editor(s). *Problem Wounds: The Role of Oxygen*. New York: Elsevier, 1988:65–123.

Marx 1990
Marx RE, Ehler WJ, Tayapongsak P. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. *American Journal of Surgery* 1990;**160**:519–24.

Mathieu 2006
Mathieu D. *Handbook on Hyperbaric Medicine*. 1st Edition. Dordrecht, Netherlands: Springer, 2006.

Neuman and Thom 2008
Neuman T, Thom S. *Physiology and Medicine of Hyperbaric Oxygen Therapy*. 1. Philadelphia, PA: Saunders, 2008.

Parmar 1998
Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analysis of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**: 2815–34. [: 9921604]

Pavy 1995
Pavy JJ, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, et al.EORTC Late Effects Working Group. Late effects toxicity scoring: the SOMA scale. *Radiotherapy and Oncology* 1995;**35**:11-5.

Rubin 1968
Rubin P, Casarrett GW. *Clinical Radiation Pathology*. Vol. **1**, Philadelphia, PA: WB Saunders, 1968:58–61.

Rubin 1984
Rubin P. Late effects of chemotherapy and radiation therapy: a new hypothesis. *International Journal of Radiation Oncology, Biology and Physics* 1984;**10**:5–34.

Stone 2003
Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. *Lancet Oncology* 2003;**4**(9):529–36. [MEDLINE: 12965273]

Thompson 1999

Thompson IM, Middleton RG, Optenberg SA, Austenfeld MS, Smalley SR, Cooner WH, et al.Have complication rates decreased after treatment for localized prostate cancer? . *Journal of Urology* 1999;**162**(1):107–12. [MEDLINE: 10379751]

Trott 1984

Trott KR. Chronic damage after radiation therapy: challenge to radiation biology. *International Journal of Radiation Oncology, Biology and Physics* 1984;**10**:907–13.

Waddell 1999

Waddell BE, Rodriguez-Bigas MA, Lee RJ, Weber TK, Petrelli NJ. Prevention of chronic radiation enteritis. *Journal of the American College of Surgeons* 1999;**189**(6):611–24. [MEDLINE: 10589598]

WHO 2004

World Health Organization. Cancer. http://www.who.int/cancer/en/ 2004.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Annane 2004

Methods	Multicentre RCT with central computerised allocation concealment and patient/outcome assessor blinding
Participants	Patients with overt ORN for at least 2 months despite antibiotics, local irrigation and surgery
Interventions	Control: 9% oxygen breathing at 2.4 ATA for 90 minutes 30 times over 3 weeks. If an operation was required, a further 10 treatments were given postoperatively HBOT: 100% oxygen on the same schedule
Outcomes	Resolution of the problem, establishment of mucosal cover
Notes	This trial did not test the standard therapeutic approach because most participants were deemed to have failed if they required operative therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Clear description. "The random allocation sequence (1:1) was generated by the statistician ...using a computer-generated list equilibrated every four patients."
Allocation concealment (selection bias)	Low risk	"Patients were assigned to their treatment group by the pharmacist, and the allocation sequence remained concealed for all investigators, patients, nursing staff, and the members of the SEMB throughout the study period."
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double blind, and there was a convincing description of the sham procedure: "HBO was performed using a multiplace chamber (CXPRO; COMEX, Marseilles, France) pressurized with compressed air, and, at plateau, the patients received, via a tight-fitting oronasal mask, either 100% oxygen without oxygen pauses (active treatment) or a gas containing 9% oxygen and 91% nitrogen (the placebo), which yielded similar arterial oxygenation than breathing room air at 1 ATA."

Annane 2004 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blind, and there was a convincing description of the sham procedure: "HBO was performed using a multiplace chamber (CXPRO; COMEX, Marseilles, France) pressurized with compressed air, and, at plateau, the patients received, via a tight-fitting oronasal mask, either 100% oxygen without oxygen pauses (active treatment) or a gas containing 9% oxygen and 91% nitrogen (the placebo), which yielded similar arterial oxygenation than breathing room air at 1 ATA."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All study outcomes were blindly assessed by the same surgeon (P.A.)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in final outcome. "Among the 68 randomly assigned patients, at 1 year there were six (19.3%) of 31 patients who had recovered in the HBO arm and 12 (32. 4%) of 37 in the placebo arm."
Selective reporting (reporting bias)	Low risk	All outcomes indicated have been reported in this paper.
Other bias	High risk	The nature of the primary outcome is very unusual. The issue is discussed in the text

Clarke 2008

Methods	Multicentre RCT with central computerised allocation concealment and patient/outcome assessor blinding
Participants	150 patients with a 3-month history of radiation proctitis unresponsive to therapy
Interventions	Control: Air breathing at 1.1 ATA for 90 minutes 30 times over 6 weeks. Sham compression to trivial pressure and return HBOT: 100% oxygen at 2.0 ATA for 30 or 40 sessions over 6 to 8 weeks
Outcomes	Healing or significant improvement LENT-SOMA Scores QoL assessment
Notes	Full report of the proctitis group of this study
Risk of bias	

Clarke 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Biostatisticians at the University of South Carolina generated the randomization sequence, which was uploaded into, and concealed within, the study database software. The patients were randomly assigned (1:1) to receive HBO or normobaric air, using a "blocking" process. The block size was four and was equally stratified with two of each treatment options (A or B)."
Allocation concealment (selection bias)	Low risk	Apparent from the following description. "The randomization sequence became available to the unblinded local principal investigator only on irretrievable entry of each patient's demographic information, medical history, and clinical characteristics."
Blinding (performance bias and detection bias) All outcomes	Low risk	There is a good description of the sham treatment. "For patient blinding purposes, Group 2 patients underwent a brief compression to 1.34 ATA at the beginning of each treatment. The chamber was then slowly decompressed from 1.34 to 1.1 ATA." "Reassessment, after 30 treatment sessions, was undertaken by the referring physician, who remained unaware of the allocation."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	There is a good description of the sham treatment. "For patient blinding purposes, Group 2 patients underwent a brief compression to 1.34 ATA at the beginning of each treatment. The chamber was then slowly decompressed from 1.34 to 1.1 ATA"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Reassessment, after 30 treatment sessions, was undertaken by the referring physician, who remained unaware of the allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full follow-up at the end of treatment. Reasonable rate of attrition and equal across groups. "Of the 150 patients, 120 completed the protocol (Fig. 2). At 1 year, 5 patients (4%) had died and 9 (8%) had been lost to follow-up."

Clarke 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	No missing outcomes
Other bias	Unclear risk	Randomised data were not available for outcomes beyond the end of therapy because the study was then unblinded and cross-over offered to those not in the active-treatment group

Gothard 2010

Methods	Multicentre RCT - 2:1 ratio of allocation to study versus control group
Participants	58 patients with unilateral arm lymphoedema of a greater than 15% increase in arm volume and persisting for at least 3 months with good treatment for lymphoedema
Interventions	All patients in both groups received 'good standard care' for lymphoedema and in the active group the participants also received HBOT at 2.4 ATA with 90 minutes of 100% oxygen breathing for a total of 30 treatment sessions over 6 weeks
Outcomes	Change in arm volume and QoL assessment at 1 year
Notes	Trial prompted by non-random observation and the results of Pritchard 2001

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation run from central allocation body: "Research volunteers were randomised with a ratio of 2:1 (treatment:control) ...by a telephone call to the randomisation service of The Institute of Cancer Research Clinical Trials & Statistics Unit."
Allocation concealment (selection bias)	Low risk	Randomisation made after consent: "Research volunteers were randomised with a ratio of 2:1 (treatment:control) after confirmation of eligibility and consent procedure..."
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding and one of the main outcomes was QoL. Bias less likely for arm volume and other objective outcomes: "Volunteers in the treatment group were compressed to 2.4 atmospheres absolute (ATA) (243 kPa) in a hyperbaric chamber ..... Volunteers in the control group continued best stan-

Gothard 2010 (*Continued*)

		dard care for lymphoedema."
Blinding of participants and personnel (performance bias) All outcomes	High risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk of arm volume, quantitative lymphoscintigraphy and dielectric constant meter measurements to determine ongoing lymphoedema
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account and most patients were followed up at 1 year: "Of the 58 patients randomised, baseline assessments were done in 53 (91.4%): 17 control and 36 HBO. Of the 53 patients with baseline assessments, 46 had 12-month assessments (86.8%): 16 control and 30 HBO. Reasons why patients did not have assessments at baseline and 12 months are shown in Fig. 1."
Selective reporting (reporting bias)	Low risk	No evidence for this
Other bias	Low risk	No indication of other bias

Hulshof 2002

Methods	Randomised trial using random number table with allocation concealment but no blinding. Randomised in matched pairs
Participants	7 patients with cognitive deficits present at least 1.5 years after irradiation of the brain with at least 3000 cGy
Interventions	Control: Nil specific HBOT: 100% oxygen at 3 ATA for 115 minutes for 30 sessions over 6 weeks (5 days out of 7 each week)
Outcomes	Neuropsychiatric testing
Notes	Very low power study with many outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hulshof 2002 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	The actual method used is not clear. "patients were randomly assigned to an experimental group who were treated immediate (immediate group) and a control group with delayed treatment (delayed group). The randomization was blinded and performed by an independent employee at the neurology department."
Allocation concealment (selection bias)	Unclear risk	Implied but not clearly described. "patients were randomly assigned to an experimental group who were treated immediate (immediate group) and a control group with delayed treatment (delayed group). The randomization was blinded and performed by an independent employee at the neurology department."
Blinding (performance bias and detection bias) All outcomes	High risk	No attempt at blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt at blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt at blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses at reporting "All seven eligible patients completed the full period of 30 HBO sessions as well as the three neuropsychological tests."
Selective reporting (reporting bias)	Low risk	No missing outcomes
Other bias	Unclear risk	Very small trial with very low power. "The immediate group consisted of four patients and the delayed group of three patients."

Marx 1985

Methods	Multicentre randomised trial. No details of methodology for randomisation, allocation concealment or blinding
Participants	74 patients requiring tooth extraction in a field irradiated with at least 6000 cGy more than 6 months and less than 15 years previously. Also excluded with penicillin or HBOT contraindications, active tumour present, recent chemotherapy or concurrent disease (e. g. diabetes) that might affect wound healing
Interventions	Control: teeth extracted in standard way with 1 million units penicillin pre-extraction and 500 mg four times each day for 10 days postextraction HBOT: 20 preoperative treatment sessions at 2.4 ATA for 90 minutes daily 5 or 6 days each week, followed by 10 further sessions postoperatively
Outcomes	Development of clinical ORN with non-healing at 6 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information apart from use of the word "randomized"
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	No information given

Marx 1999a

Methods	Described as randomised. No details concerning blinding or allocation concealment
Participants	104 patients requiring hemimandibular jaw reconstruction in tissue beds exposed to at least 6400 cGy radiotherapy. No other specific exclusions
Interventions	Control: not state HBOT: 20 preoperative treatment sessions at 2.4 ATA for 90 minutes daily 5 days each week, followed by 10 further sessions postoperatively
Outcomes	"Success" defined as achievement of continuity, restoration of alveolar bone height, restoration of osseous bulk, restoration of arch form, maintenance of bone form for 18 months and restoration of facial contours Complication rate (infection or dehiscence)
Notes	Sketchy account within a textbook chapter written by the author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information apart from use of the word "randomized"
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	No information given

Marx 1999b

Methods	Described as randomised. No details concerning blinding or allocation concealment
Participants	160 patients requiring major soft tissue surgery or flaps into an irradiated area (> 6400 cGy). No other specific exclusions
Interventions	Control: not stated HBOT: 20 preoperative treatment sessions at 2.4 ATA for 90 minutes daily 5 days each week, followed by 10 further sessions postoperatively
Outcomes	Wound infection, dehiscence, delayed healing
Notes	Sketchy account within a textbook chapter written by the author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information apart from use of the word "randomized"
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	No information given

Pritchard 2001

Methods	Randomised, allocation concealed with blinding of outcome assessors and patients
Participants	34 patients with established radiation-related brachial plexopathy, median duration 3 years. Subjects with active tumour or contraindications to HBOT excluded

Pritchard 2001 (*Continued*)

Interventions	Control: 100 minutes at 2.4 ATA breathing 41% oxygen to simulate 100% oxygen at 1 ATA, daily 5 days per week to a total of 30 sessions HBOT: 100% oxygen breathing on the same schedule	
Outcomes	Sensory thresholds, QoL scores, McGill pain Score, lymphoedema resolution	
Notes	Many other outcomes reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Research volunteers were randomized on the first day of treatment by a telephone call to the Clinical Trials & Statistics Unit, Institute of Cancer Research"
Allocation concealment (selection bias)	Low risk	Allocation under the control of a remote officer who was consulted prior to the first treatment
Blinding (performance bias and detection bias) All outcomes	Low risk	There was use of a convincing sham protocol. "Research volunteers randomized to the HBO2 group were compressed to 2.4 ATA (243 kPa) in the multiplace category 1 hyperbaric chamber ... Individuals allocated to the control group accompanied the HBO2 group patients and experienced the same number and type of pressure exposures."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The breathing system of the hyperbaric chamber was configured so that patients were unaware of the group to which they were allocated."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All investigators (except the operators of the hyperbaric chamber and the trial statistician) remained blind to treatment assignments until the final analysis."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although there was high loss to final assessment, there seemed equal losses in both groups and this was unlikely due to the treatment given. "Only 1/72 assessments over 12 months of planned follow up was missed. Nineteen of 34 (56%) patients attended for repeat neurophysiological test-

Pritchard 2001 (*Continued*)

		ing in September 2000, at a minimum of 24 months post-hyperbaric therapy."
Selective reporting (reporting bias)	Low risk	No missing outcome reports
Other bias	Low risk	No indication of other bias

Schoen 2007

Methods	Unblinded RCT
Participants	26 patients with a history of irradiation for a primary tumour of the head and neck who were suitable for dental implants in the lower jaw
Interventions	All received perioperative antibiotics and the HBOT group received 20 sessions on 100% oxygen at 2.5 ATA for 80 minutes daily before operation and for 10 days after operation
Outcomes	Postoperative complications, implant survival at 1 year, periodontal health indicators, functional assessment and QoL
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A computer program was used for randomization of the patients."
Allocation concealment (selection bias)	Low risk	Not specifically stated, but the implication is clear that allocation only took place after consent: "Patients who agreed with treatment were randomized in two groups."
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding and some outcomes are subjective (e.g. QoL) "These patients either received peri-operative antibiotics or antibiotics in combination with HBO treatment."
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no attempt to blind patients or those delivering care. Some outcomes are subjective (e.g. QoL) "These patients either received peri-operative antibiotics or antibiotics in combination with HBO treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor may have been unaware of allocation: "All clinical assessments were performed by the investigator (PJS) who was not involved in treatment of the patients."
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant losses to follow-up. "Two patients past (sic) away during the osseointegration because of medical complications not

Schoen 2007 (*Continued*)

		related to the implant surgery. In 23 patients implant-retained overdentures were fabricated, while in one patient no prosthesis could be made because of loss of all implants related to development of osteoradionecrosis. At the 1 year evaluation, six patients were lost to follow-up due to serious illness not related to implant surgery."
Selective reporting (reporting bias)	Unclear risk	No indication that outcome measures have not been reported
Other bias	Low risk	No indication of other bias

Sidik 2007

Methods	Unblinded RCT designed to evaluate the effect of HBOT on QoL after pelvic irradiation
Participants	Stage I to IIIB carcinoma of the cervix who had undergone irradiation
Interventions	There was no sham intervention. Those randomised to HBOT received 20 treatments but the exact protocol is not given
Outcomes	Symptom severity scale (LENT-SOMA) and Karnofsky QoL assessment
Notes	Poorly reported trial with no control therapy or blinding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Little information "The block randomisation was performed."
Allocation concealment (selection bias)	Unclear risk	No information on this
Blinding (performance bias and detection bias) All outcomes	High risk	No attempt at blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt at blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt at blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Significant loss to follow-up at 6 months with several patients dying of their primary problem

Sidik 2007 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Insufficient information is given to be certain
Other bias	Unclear risk	Poor reporting makes an assessment difficult

Teguh 2009

Methods	Unblinded RCT
Participants	19 patients with a diagnosis of nasopharyngeal or oropharyngeal carcinoma and treated with radiotherapy (47 to 70 Gy) with or without chemotherapy. HBOT given 2 days after completion of radiotherapy/chemotherapy
Interventions	100% oxygen at 2.5 ATA for 90 minutes daily for 30 sessions over 6 weeks, no sham therapy
Outcomes	QoL estimates, dryness of mouth
Notes	Trial stopped early because of slow recruitment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Seems reliable from the description. "Patients were randomized by the trial office..... by use of a block of several randomized sizes. Patients were stratified by tumor site (i.e., oropharynx or nasopharynx) and treatment modality (i.e., IMRT or Cyberknife/ Brachytherapy or postoperative radiotherapy)."
Allocation concealment (selection bias)	Low risk	"This randomization took place directly after inclusion of the patients in the study."
Blinding (performance bias and detection bias) All outcomes	High risk	Subjective outcome and no attempt at blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	All patients and treating staff aware of allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention that outcome assessor was blinding and this seems unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up

Teguh 2009 (*Continued*)

Selective reporting (reporting bias)	Low risk	No evidence for missing outcomes
Other bias	Low risk	No evidence of other biases, but relatively poor methodological reporting

ATA: atmospheres absolute
Brachial plexopathy: poor functioning of the nerves going through the armpit to supply the arm and resulting in loss of sensation, muscle power and function in the arm.
cGy: Centi-GreyHBOT: hyperbaric oxygen therapy
LENT-SOMA: Late Effects Normal Tissues - Subjective, Objective, Management, Analytic
ORN: osteoradionecrosis
QoL: quality of life
RCT: randomised controlled trial

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

Study	Reason for exclusion
Carl 2001	Case series only, no randomised comparator
Coulthard 2002	Systematic review - no new data
Denton 2002	Systematic review - no new data
Gal 2003	Retrospective cohort study
Granstrom 1999	Case control study - not randomly allocated
Maier 2000	Retrospective cohort study
Niimi 1997	Cohort study
Tobey 1979	RCT but no quantitative data given. Both groups received some HBOT (1.2 ATA versus 2.0 ATA)

ATA: atmospheres absolute
HBOT: hyperbaric oxygen therapy
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

DAHANCA 2011

Methods	RCT
Participants	Established mandibular ORN
Interventions	HBOT
Outcomes	Complete resolution or radiographic evidence only
Notes	

HOPON 2011

Methods	RCT
Participants	Patient requiring surgery in an irradiated mandible
Interventions	HBOT
Outcomes	Prevention of ORN
Notes	

HBOT: hyperbaric oxygen therapy
ORN: osteoradionecrosis
RCT: randomised controlled trial

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

Clarke 2004b

Trial name or title	Hyperbaric Oxygen for Radiation Tissue Injury Study (HORTIS)
Methods	RCT (five separate pathological groups)
Participants	Patients with radiation tissue injury in different anatomical locations, plus one group of patients scheduled for surgery in an irradiated area (prevention group)
Interventions	HBOT
Outcomes	Site specific healing
Starting date	1999
Contact information	Clarke RE

Notes	

HBOT: hyperbaric oxygen therapy
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Death

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 1 year	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.13, 5.61]

Comparison 2. Complete resolution of problem

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score change at 1 year	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Proctitis	1	120	Risk Ratio (M-H, Fixed, 95% CI)	9.65 [0.55, 170.66]
1.2 Hemimandibular reconstruction	1	104	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.14, 1.75]
1.3 Brachial plexus radiation neuropathy	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Osteoradionecrosis	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.25, 1.40]
2 Sensitivity analysis for missing data in proctitis (best case)	1	150	Risk Ratio (M-H, Fixed, 95% CI)	33.0 [2.02, 540.22]
3 Sensitivity analysis for missing data in proctitis (worst case)	1	150	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.12, 0.81]
4 Development of osteoradionecrosis following dental implant	1	26	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 67.51]

Comparison 3. Complete resolution or significant improvement of problem

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete or significant improvement	1	119	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.03, 2.86]
2 Sensitivity analysis for missing data in proctitis - (best case)	1	150	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [1.66, 4.49]
3 Sensitivity analysis for missing data proctitis - (worst case)	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.47, 0.93]

Comparison 4. Improvement in mean LENT-SOMA score

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean LENT-SOMA score at 3 months	1	150	Mean Difference (IV, Fixed, 95% CI)	2.39 [0.89, 3.89]

Comparison 5. Resolution of pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score change at end of treatment	1	34	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Pain score change at 1 year	1	34	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Resolution of swelling

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement of lymphoedema	1	34	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 97.00]
2 Relative reduction in arm volume (affected versus non-affected)	1	86	Mean Difference (IV, Fixed, 95% CI)	2.6 [-13.54, 18.74]
3 Proportion with more than 8% reduction in arm volume	1	46	Odds Ratio (M-H, Fixed, 95% CI)	1.86 [0.42, 8.15]

Comparison 7. Quality of Life and Functional Outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SF-36 general health at 1 year	1	34	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-18.95, 14.35]
2 Physical functioning score at 1 year	1	34	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-19.40, 11.40]

Comparison 8. Osteoradionecrosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete mucosal cover	3	246	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.09, 1.55]
2 Establishment of bony continuity	1	104	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.14, 1.75]
3 Resolution of sinus tract	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Successful healing of tooth sockets after tooth extraction	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.08, 1.68]
5 Bone loss around implant site	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.67, 0.47]

Comparison 9. Head and Neck

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Wound dehiscence	2	264	Risk Ratio (M-H, Random, 95% CI)	4.23 [1.06, 16.83]
1.1 Hemimandibular reconstruction (bone and soft tissue)	1	104	Risk Ratio (M-H, Random, 95% CI)	2.2 [0.82, 5.89]
1.2 Complex soft-tissue grafts/ flaps	1	160	Risk Ratio (M-H, Random, 95% CI)	8.67 [2.73, 27.49]
2 Loss of dental implant	1	26	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.59, 10.64]

Comparison 13. Neurological tissue

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Warm sensory threshold 1 week after treatment (degrees Centigrade change from baseline)	1	34	Mean Difference (IV, Fixed, 95% CI)	1.12 [-1.90, 4.14]
2 Warm sensory threshold at 1 year	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-3.97, 2.23]
3 Net number of significantly improved neuropsychological tests at 3 months (25 tests total)	1	7	Mean Difference (IV, Fixed, 95% CI)	2.00 [-1.60, 5.60]
4 Net number of significantly improved neuropsychiatric tests at 6 months	1	7	Mean Difference (IV, Fixed, 95% CI)	1.0 [-3.55, 5.55]

ADDITIONAL TABLES

Table 1. The LENT-SOMA Scales - Conceptual summary

(S)ubjective	(O)bjective	(M)edical management	(A)nalytic
The injury from the patient point of view. May involve interview, diary or questionnaire depending on the system to be used	Morbidity assessed objectively by clinician during physical examination	The active steps that have been taken in order to ameliorate the symptoms	Diagnostic and imaging tools used to further objectively define the level of injury

WHAT'S NEW

Last assessed as up-to-date: 22 March 2012.

Date	Event	Description
29 March 2012	New citation required but conclusions have not changed	Searches re-run March 2011 and three new studies identified.
11 January 2012	New search has been performed	'Risk of bias' and 'Summary of findings' tables added. Study flow figure added. No major change to conclusions

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 3, 2005

Date	Event	Description
23 August 2008	New search has been performed	Two new trials identifed and added to review when searches were re-run in August 2008
26 April 2008	Amended	Converted to new review format.
23 May 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Michael Bennett: principal author, conception, search strategy and execution, data extraction and critical appraisal, hyperbaric medicine content expert, statistical analysis.

John Feldmeier: co-author, data extraction and critical appraisal, radiation oncology and hyperbaric medicine content expert.

Neil Hampson: co-author, editorial advice, data extraction and critical appraisal, hyperbaric medicine content expert.

Chris Milross: co-author background, radiation oncology content expert.

Robert Smee: editorial advice, radiation oncology content expert.

DECLARATIONS OF INTEREST

None known. Bennett and Hampson are hyperbaric physicians who regularly treat patients with LRTI, while Feldmeier has previous hyperbaric experience. Milross, Feldmeier and Smee are radiation oncologists who refer patients with LRTI for HBOT.

SOURCES OF SUPPORT

Internal sources

- No source of support, Not specified.

External sources

- No external source of support, Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Anus Neoplasms [radiotherapy]; Head and Neck Neoplasms [radiotherapy]; Hyperbaric Oxygenation [*methods]; Neoplasms [*radiotherapy]; Osteoradionecrosis [prevention & control]; Radiation Injuries [prevention & control; *therapy]; Randomized Controlled Trials as Topic; Rectal Neoplasms [radiotherapy]

MeSH check words

Humans