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Hyperbaric oxygen therapy for late radiation tissue injury (Review)

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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 LRTI developing months or years later. HBOT has been suggested 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 strategy
We searched The Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3, 2004, MEDLINE, EMBASE, CINAHL and DORCTHIM (hyperbaric RCT register) in September 2004.

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

Data collection and analysis
Three reviewers independently evaluated the quality of the relevant trials using the guidelines of the Cochrane Handbook Clarke 2003 and extracted the data from the included trials.

Main results
Six trials contributed to this review (447 participants). For pooled analyses, investigation of heterogeneity suggested important variability between trials. From single studies there was a significantly improved chance of healing following HBOT for radiation proctitis (relative risk (RR) 2.7, 95% confidence Interval (CI) 1.2 to 6.0, P = 0.02, numbers needed to treat (NNT) = 3), and following both surgical flaps (RR 8.7, 95% CI 2.7 to 27.5, P = 0.0002, NNT = 4) and hemimandibulectomy (RR 1.4, 95% CI 1.1 to 1.8, P = 0.001, NNT = 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, NNT = 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 osteoradionecrosis 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 also be undertaken. There is no useful information from this review regarding the efficacy or effectiveness of HBOT for other tissues.
Hyperbaric oxygen (HBO) may improve radiation injuries of the head, neck and bowel. It also appears to reduce the chance of bone death following tooth extraction.

There is a risk of serious complications developing after radiation treatment for cancer (late radiation tissue injury (LRTI)). Hyperbaric oxygen therapy (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 six randomised trials with a limited number of patients. Further research is needed.

Hyperbaric oxygen therapy for late radiation tissue injury (Review)

Cancer is a significant global health problem. According to World Health Organization 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 radiation therapy (Jeimal 2002), and of these, about 50% will be long-term survivors. While radiation therapy 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 radiation therapy, 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, 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 late radiation injuries 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. 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.

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 one 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.

The intermittent application of HBO 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 HBO six months later. The 2 control groups showed no improvement while a series of 20 sessions at 2.4 atmospheres absolute (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 (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).

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 recent semi-quantitative review, Feldmeier and Hampson located 71 such reports involving a total of 1193 patients across 8 different tissues (Feldmeier 2002). In these patients, for whom conservative treatment had failed to improve symptoms, there were clinically significant improvements 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. A recent comprehensive review fails to support these concerns (Feldmeier 2003).

**O B J E C T I V E S**

The objectives of this review were to determine the efficacy and safety of HBOT in the treatment of patients with late radiation tissue injury.

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?

**C R I T E R I A F O R C O N S I D E R I N G S T U D I E S F O R T H I S R E V I E W**

**Types of studies**

Randomised and pseudo-RCTs that compared the effect of a regimen including HBOT on any form of late radiation tissue injury, with any treatment regimen not including HBOT.

**Types of participants**

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

**Types of intervention**

We accepted trials comparing regimens which 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 mins and 120 mins 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:

- (1) Survival
- (2) Complete resolution of necrosis or tissue damage
- (3) Improvement in LENT-SOMA scale

[The LENT-SOMA scales (Late Effects Normal Tissues - Subjective, Objective, Management, Analytic) 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 01.]

- (4) Resolution of pain
- (5) Resolution of swelling
- (6) Improvement in quality of life (QOL) and/or function

(7) Osteoradionecrosis (ORN)
Primary outcome measures:
(a) Healing with complete soft tissue coverage over bone
(b) Resolution of sinus tract between bone and skin or mucosa
(c) Resolution of fracture or re-establishment of bony continuity
(d) Development of ORN in tooth socket following extraction

Secondary outcome measures:
(e) Improvement in X-Ray appearance

(8) Head and neck soft tissues
Primary outcome measures:
(a) Wound dehiscence (breakdown of a surgical wound)
(b) Surgical removal of larynx
(c) Major vessel bleeding

Secondary outcome measures:
(d) Speed of wound healing
(e) Improvement in swelling or 'woodiness' of tissue
(f) Reversal of tracheostomy (surgical breathing hole in the trachea)

(9) Urinary bladder
Primary outcome measures:
(a) Resolution of bleeding
(b) Removal of bladder and urine diversion procedures

Secondary outcome measures:
(c) Improved cystoscopic appearance
(d) Frequency
(e) Dysuria (pain on passage of urine)

(10) Chest wall
Nil additional to those listed under 'All anatomical areas'.

(11) Bowel
Primary outcome measures:
(a) Resolution of bleeding
(b) Operations on the bowel such as colostomy, ileostomy or bowel resection

Secondary outcome measures:
(c) Improvement in pain score

(12) Neurological tissue
Primary outcome measures:
(a) Improvement in objective motor function
(b) Improvement in visual acuity

Secondary outcome measures:
(c) Improvement in sensory function
(d) Improvement in functional ability or activities of daily living
(e) Improvement in neuropsychiatric testing
(f) Improvement in X-ray or scan appearance
(g) Reduction in steroid dose

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

Adverse events of HBOT
(a) Recurrence of tumour (locally or remote)
(b) Visual disturbance (short and long term)
(c) damage from pressure (aural, sinus or pulmonary barotrauma, in the short and long-term)
(d) Oxygen toxicity (short-term)
(e) Withdrawal from treatment for any reason
(f) Any other recorded adverse effect

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Gynaecological Cancer Group search strategy

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

Electronic searches
We searched: CENTRAL (The Cochrane Library August 2004), MEDLINE (1966 to August 2004), EMBASE (1980 to August 2004), CINAHL (1982 to August 2004) and an additional database developed in our hyperbaric facility, The Database of Randomised Trials in Hyperbaric Medicine (Bennett 2004). The search strategy was broad and the keywords in the following strategies were adapted as appropriate. The EMBASE and MEDLINE (OVID) strategies are given in Table 02.

In addition we made a systematic search for relevant controlled trials in specific hyperbaric literature sources as follows.

- 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 randomized trials.

- Handsearch of relevant hyperbaric textbooks (Kindwall, Jain, Marroni, Bakker, Bennett and Elliot), journals (Undersea and Hyperbaric Medicine, Hyperbaric Medicine Review, South Pacific Underwater Medicine Society (SPUMS) Journal, European Journal of Hyperbaric Medicine and Aviation, 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.
METHODS OF THE REVIEW

Data retrieval and management
One reviewer (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 reviewers (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 reviewers identified them as appropriate. Retained studies were retrieved in full and reviewed independently by three reviewers, all with content expertise in HBOT, one with content expertise in radiation oncology (JF). In addition one of the reviewers (MB) has expertise in clinical epidemiology. Reviewers recorded data using the data extraction form developed for this review.

Data extraction
Each reviewer 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 reviewers and no disputed trials required referral to the Review Group contact editor for appraisal.

Quality assessment
Study quality was assessed using an adaptation of the method outlined in Schulz (Schulz 1995), and recommendations made for inclusion or exclusion from the review. Results from the study quality assessment are presented in a descriptive manner. The following characteristics were assessed:

Adequacy of the randomization process:
A- Adequate sequence generation is reported using random number tables, computer random number generator, coin tossing, or shuffling;
B- Did not specify one of the adequate reported methods in (A) but mentioned randomization method;
C- Other methods of allocation that appear to be unbiased.

Adequacy of the allocation concealment process:
A- Adequate measures to conceal allocations such as central randomization; serially numbered, opaque, sealed envelopes; or other description that contained convincing elements of concealment;
B- Unclearly concealed trials in which the author either did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the categories in (A);
C- Inadequately concealed trials in which method of allocation is not concealed such as alternation methods or use of case record numbers.

Potential for selection bias after allocation:
A- Trials where an intention-to-treat analysis is possible and few losses to follow-up are noted;
B- Trials which reported exclusions (as listed in A but exclusions were less than 10%);
C- No reporting on exclusions or exclusions greater than 10% or wide differences in exclusions between groups.

Level of masking (treatment provider, patient, outcome assessor):
A- Double or triple-blind;
B- Single-blind;
C- Non-blind.

These four factors were considered for possible sensitivity analysis.

Analyses
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 intention-to-treat analysis where possible and reflect efficacy in the context of randomized 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 was available. For dichotomous outcomes RR was used. For continuous data, the mean difference (MD) between treatment and control arms in each trial was calculated and aggregated using inverse variance weights to estimate an overall MD and its 95% 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 (NNT) and number needed to harm (NNH) with 95% CI as appropriate, using the formula NNT = 1/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 mean difference (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:
(4) 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.

(5) 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.

Sensitivity analyses
We intended to perform sensitivity analyses for missing data and study quality where appropriate.

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 whilst all those missing from the control group did. The worst case scenario was the reverse.

Study quality
If appropriate, we had planned to conduct a sensitivity analysis by study quality based on the presence or absence of a reliable random allocation method, concealment of allocation and blinding of participants or outcome assessors.

Heterogeneity
Heterogeneity was assessed using the I² statistic and consideration given to the appropriateness of pooling and meta-analysis.

Subgroups
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

DESCRIPTION OF STUDIES
We identified 103 publications apparently dealing with the use of HBOT for the treatment of LRTI. Initial examination confirmed 62 were case reports or case series, 25 were reviews or letters without new data, one was a report of a planning workshop and one was a report of animal work. These reports were excluded, leaving 14 possible randomised comparative trials. 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 other six trials were accepted into the review (Clarke 2004; Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Pritchard 2001). Marx 1999a and Marx 1999b are trials reported for the first time in a textbook. The recruitment period for these studies is not known.

The included trials were published between 1985 and 2004, and the reviewers are aware that there is a large, multicentre trial underway into the effect of HBOT on eight different manifestations of LRTI. Clarke 2004 is the first brief report of one arm of that trial. In total, these trials include data on 447 participants, 224 receiving HBOT and 223 control. The largest (Marx 1999b) accounts for 36% of cases. (See Table: ‘Characteristics of included studies’).

Where sex was specified, the trials enrolled more females than males (Pritchard 2001 enrolled 34 participants, all female; Hulshof 2002 six females and one male). With regard to age, Pritchard 2001 enrolled participants from age 40 to 79 years and in Hulshof 2002 the average age was 46 years. Two studies did not specify any such characteristics except prior exposure to 6400 cGy in the area under investigation (Marx 1999a; Marx 1999b). The other four studies specified exclusion of those unfit for compression or the presence of residual tumour, while Marx 1985 also excluded those with penicillin sensitivity, recent chemotherapy or concurrent disease known to affect wound healing. No details of prior therapy for the pathology under study were given, while Marx 1985 specified a minimum prior radiation dose of 6000 cGy at least six months prior to enrollment. Clarke 2004 entered participants with radiation proctitis, Hulshof 2002 those with cognitive deficits following brain irradiation with at least 30 Gy, Pritchard 2001 radiation-induced brachial plexus lesions, Marx 1999a candidates for hemimandibular jaw reconstruction, Marx 1999b candidates requiring major soft tissue surgery or flaps, and Marx 1985 participants requiring tooth extraction.

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 2004) and the highest 3.0 ATA (Hulshof 2002), while all other trials utilised 2.4 ATA. Treatment periods for each session ranged from 90 minutes (Marx 1985; Marx 1999a; Marx 1999b) to 120 minutes (Clarke 2004). All trials administered a total of 30 treatments except Clarke 2004, where there was an option to continue to 40 treatments.

Marx 1985 involved a comparator treatment of penicillin for 10 days, while there were no active comparator regimens in the other trials. Two trials administered a blinded sham therapy (Clarke 2004; Pritchard 2001). Details are given in the table 'Characteristics of included studies'.
The follow-up periods varied between three weeks following the treatment course (Marx 1999b), three months (Clarke 2004), six months (Hulshof 2002; Marx 1985) and one year (Pritchard 2001). 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, 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: self-rated memory and dexterity (Hulshof 2002), sensory action potentials (Pritchard 2001), post-surgical complication rate (Marx 1999a) and wound infection rate (Marx 1999b).

**METHODOLOGICAL QUALITY**

Details of the quality assessment are given in the table ‘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. Although Clarke 2004 is an abstract only, this trial is known to the reviewers and many details have been provided through personal communication.

**Allocation concealment**

Allocation concealment was adequately described in three studies (Clarke 2004; Hulshof 2002; Pritchard 2001), all three using 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 two studies (Clarke 2004; Pritchard 2001), both employing a computer generated random number table, but not in the other four.

**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 four studies specified exclusion of those unfit for compression. No details of prior therapy for the pathology under study were given, while Marx 1985 specified a minimum prior radiation dose of 6000 cGy at least six months prior to enrollment.

**Blinding**

Two studies utilised a sham therapy in order to mask subjects and outcome assessors to HBOT (Clarke 2004; Pritchard 2001), while no sham was employed in the remaining four studies (Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b). No author formally tested the success of their blinding strategy.

**Patients lost to follow-up**

Five studies did not report any losses to follow-up or violation of the study protocol (Hulshof 2002; Marx 1985; Marx 1999a; Marx 1999b; Pritchard 2001). Clarke 2004 lost seven control subjects and four HBOT group subjects, and these subjects we excluded from the analysis reported in the abstract. 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 intention to treat analysis (two subjects in the HBOT group did not complete therapy, but were included in analysis). Four of the remaining five studies reported full follow-up and did not report any protocol violation (see above).

**RESULTS**

**Combined anatomical areas**

**Primary outcomes**

(1) Death (comparison 01)

No trial reported any data on this outcome.

(2) Complete resolution of tissue damage or necrosis (comparison 02)

(a) Complete resolution of clinical problem at three months (comparison 02, outcomes 01, 02, 03)

Three trials reported this outcome (Clarke 2004; Marx 1999a; Pritchard 2001), involving 172 participants (39% of the total participants in this review), with 86 randomised to both HBOT and control arms. Overall, 64 (74%) of participants in the HBOT arm achieved resolution, versus 40 (47%) in the control group. Analysis for heterogeneity suggested a high proportion of variability between trials was not due to sampling variability ($I^2 = 65\%$), and so this comparison was made using a random effects model with stratification by tissue type involved (other subgroup analyses did not separate these studies). Further, one study (Pritchard 2001) did not report any participants with resolution, so could not contribute to the analysis.

There was a significantly improved probability of resolution with the administration of HBOT for both radiation proctitis (RR 2.7, 95% CI 1.2 to 6.0, $P = 0.02$) (Clarke 2004), and hemimandibulectomy (RR 1.4, 95% CI 1.1 to 1.8, $P = 0.001$, (Marx 1999a). The result for proctitis was however, sensitive to the allocation of dropouts (best case: RR 3.3, 95%CI 1.5 to 7.3, $P = 0.002$; worst case: RR 1.2, 95% CI 0.7 to 2.2, $P = 0.4$). For proctitis, 16 participants (47%) achieved resolution of their problem following HBOT versus six participants (18%) in the control group, suggesting the number needed to treat with HBOT to achieve one extra subject with a resolved problem was 3, (95% CI 2 to 11).
For participants requiring hemimandibulectomy, 48 participants (92%) achieved resolution following HBOT versus 34 (65%) in the control group. NNT 4, (95% CI 2 to 8).

(3) LENT-SOMA scores (comparison 03)
(a) Improvement in LENT-SOMA score at three months
Only one trial reported this outcome (Clarke 2004) involving 68 subjects (15% of the total), with 34 randomised to both HBOT and control. The mean improvement in LENT-SOMA score was greater in the HBOT group (4.7 versus 0.73), and this difference was statistically significant (WMD 4.0, 95% CI 1.7 to 6.3, P = 0.0007).

Secondary outcomes
(4) Pain scores (comparison 04)
(a) Change in pain score (0 to 100 scale) from baseline to six months after treatment (comparison 04, outcome 01)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% of the total) 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 versus 1.2). 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 04, outcome 02)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% of the total) with 17 randomised to both HBOT and control. Pain scores were reduced in both groups, but more so in the controls (-5.0 points versus -0.7). Standard deviations were not reported around these means, precluding further analysis.

5. Swelling (comparison 05)
(a) Resolution of lymphoedema in arm at six months (comparison 05, outcome 01)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% of the total) with 17 randomised to both HBOT and control. Two subjects (12%) in the HBOT arm 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) Resolution of lymphoedema in arm at 12 months (comparison 05, outcome 02)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% of the total) with 17 randomised to both HBOT and control. Twelve (65%) in the HBOT arm achieved resolution, while none in the control group did so. This difference in favour of HBOT was not statistically significant (WMD -2.3, 95% CI -19.0 to 14.4, P = 0.79).

(6) Quality of life or functional scores (comparison 06)
(a) SF-36 score for general health at 12 months (comparison 06, outcome 01)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% of the total) with 17 randomised to both HBOT and control. The mean score for general health self-rating was lower in the HBOT group (53.5 versus 57.5), but not significantly so (WMD -4.0, 95% CI -19.4 to 11.4, P = 0.61).
(b) SF-36 score for physical functioning at 12 months (comparison 06, outcome 02)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% of the total) 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 versus 57.5), but not significantly so (WMD -4.0, 95% CI -19.4 to 11.4, P = 0.61).

(7) Osteoradionecrosis
Primary outcomes
(a) Achievement of complete mucosal cover (comparison 07, outcome 01)
Two trials reported this outcome (Marx 1995a; Marx 1999a), involving 178 subjects (40% of the total), with 89 randomised to both HBOT and control arms. Eighty three (93%) of subjects in the HBOT arm achieved resolution, versus 60 (67%) in the control group. Heterogeneity did not appear to be a problem with this analysis (I² = 0%). There was a significantly improved probability of attaining mucosal cover with the administration of HBOT (RR 1.4, 95% CI 1.2 to 1.6, P < 0.001). The NNT to achieve one further case with mucosal cover with the application of HBOT is 4, (95% CI 2 to 8).

(b) Resolution of sinus tract (comparison 07, outcome 03)
No study reported data on this outcome.
(c) Establishment of bony continuity (comparison 07, outcome 02)
Only one trial contributed results to this outcome (Marx 1995a) involving 104 subjects (23% of the total), 52 randomised to both HBOT and control. Forty eight (92%) of subjects in the HBOT arm 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). The NNT to achieve one further case with bony continuity with the application of HBOT is 4, (95% CI 2 to 8).
(d) Healing of tooth sockets following extraction in irradiated field at six months (comparison 07, outcome 03)
Only one trial contributed results to this outcome (Marx 1985) involving 74 subjects (17% of the total), 37 randomised to both HBOT and control. Thirty five (87%) of subjects in the HBOT arm 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). The NNT with HBOT to achieve one further case with all tooth sockets healed is 4, (95% CI 2 to 13).

Secondary outcomes
(c) Improvement in X-Ray appearance (comparison 07, outcome 05)
No study reported data on this outcome.

8. Head and neck tissues
Primary outcomes
(a) Wound dehiscence (comparison 08, outcome 01)
Two trials reported this outcome (Marx 1999a; Marx 1999b), involving 132 subjects (60% of the total subjects in this review), with 132 randomised to both HBOT and control arms. Overall,
8 (6%) subjects in the HBOT arm 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 (I²=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). Stratification by tissue type involved confirmed the direction 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 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).

(b) Surgical removal of the larynx (comparison 08, outcome 02)
No study reported data on this outcome.

(c) Major bleeding (comparison 08, outcome 03)
No study reported data on this outcome.

Secondary outcomes
(d) Speed of wound healing (comparison 08, outcome 04)
No study reported data on this outcome.

(e) Improvements in tissue quality (comparison 08, outcome 05)
No study reported data on this outcome.

(f) Reversal of tracheostomy (comparison 08, outcome 06)
No study reported data on this outcome.

(9) Urinary bladder (comparison 9)
No study reported data on outcomes for this tissue.

(10) Chest wall (comparison 10)
No study reported data on outcomes for this tissue.

(11) Bowel (comparison 11)
No study reported data on outcomes for this tissue.

(12) Neurological tissue (comparison 12)
Primary outcomes
(a) Objective motor function (comparison 12, outcome 01)
No study reported data on this outcome.

(b) Visual acuity (comparison 12, outcome 02)
No study reported data on this outcome.

Secondary outcomes
(c) Warm sensory threshold at one week after therapy (comparison 12, outcome 03)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% of the total) with 17 randomised to both HBOT and control. The mean threshold temperature for reporting a warm sensation at one week after therapy (compared to pretreatment baseline) was reduced in the HBOT group, but not in the controls (-0.1 degree versus 1 degree). This difference was not statistically significant (WMD 1.1 degrees lower, 95% CI -1.9 to 4.1, P = 0.47).

(d) Warm sensory threshold at one year after therapy (comparison 12, outcome 04)
Only one trial reported this outcome (Pritchard 2001) involving 34 patients (8% of the total) 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 versus 1.4). This difference was not statistically significant (WMD 0.9 degrees, 95% CI -2.3 to 4.0, P = 0.47).

(e) Functional ability scores and ADL (comparison 12, outcome 05)
No study reported data on this outcome.

(f) Net number of neuropsychological tests (maximum 25 tests)
No study reported data on this outcome.

(13) Adverse events
No study reported data on these outcomes.

DISCUSSION
This review has included data from six trials investigating the use of HBOT for tissue suffering from late radiation damage, and we believe these represent all randomised human trials in this area, both published and unpublished, at the time of searching the databases. 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 toward 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 was no data reported from any randomised trials involving the use of HBOT to treat other manifestations of radiation tissue damage.
Only six trials with 447 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 19-year period up to 2004, 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.

Three trials reported on complete resolution of the clinical problem (Clarke 2004; Marx 1999a; Pritchard 2001). Results varied widely and could not be pooled. Clarke 2004 and Marx 1999a reported significant improvement in the chance of healing radiation proctitis (RR 2.7, P = 0.02, NNT 4), and following hemi-mandibulectomy and reconstruction (RR 1.4, P = 0.001, NNT 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). The Clarke 2004 analysis was also sensitive to the allocation of dropouts and we await further reporting of this trial in full. Although this trial has only been reported in abstract, the author has provided considerable methodological detail in private correspondence for this review.

Pooling data for clinical outcomes of interest could only be performed with respect to the risk of wound dehiscence. This analysis suggested some benefit from HBOT administration (RR of dehiscence with control group was 4.2 [95% CI 1.1 to 16.8], NNT 5 [95% CI 3 to 8]). This result was subject to a high proportion of variability being due to differences between trials rather than to sampling variability, and the two trials were of relatively low quality. It should be interpreted with great caution. This possible treatment effect is, however, of great clinical importance and deserves further investigation.

The incidence of adverse effects was not assessed 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 pre-treatment levels. None of the trials included in this review reported visual changes. 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.

All of these findings are subject to a potential publication bias. 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 little relevant data.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

There is some evidence that HBOT improves outcome in late radiation tissue injury affecting bone and soft tissues of the head and neck, for radiation proctitis and to prevent the development of osteoradionecrosis 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. 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. Further research is required to establish the optimum patient selection and timing of any such therapy. An economic evaluation should also be undertaken. There is no evidence of a benefit from...
HBOT for the treatment of affected neurological tissue, and to date, no useful information regarding the efficacy or effectiveness of HBOT for other tissues can be provided.

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 late radiation tissue injury. 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

Potential conflict of interest
None known. Bennett and Hampson are hyperbaric physicians who regularly treat patients with late radiation tissue injury, while Feldmeier has previous hyperbaric experience. Milross, Feldmeier and Smee are radiation oncologists who refer patients with late radiation tissue injury for HBOT.

Acknowledgements
We thank Jill Porthouse, Clare Jess and Gail Quinn of the Cochrane Gynaecological Cancer CRG for their assistance in the preparation of this review.

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External sources of support
• No sources of support supplied

Internal sources of support
• No sources of support supplied

References

References to studies included in this review
Clarke 2004 [unpublished data only]

Hulshof 2002 [published data only]

Marx 1985 [published data only]

Marx 1999a [published data only]

References to studies excluded from this review
Carl 2001

Couthard 2002
Denton 2002

Gal 2003

Granstrom 1999

Maier 2000

Niimi 1997

Tobey 1979

References to ongoing studies
Clarke 2004b
Ongoing study Starting date of trial not provided. Contact author for more information.

Additional references
Alman 2001

Bennett 2004

Clarke 2003

Davis 1988

Feldmeier 1995

Feldmeier 1998

Feldmeier 2002

Feldmeier 2003

Hills 1999

Jemal 2002

Khan 2003

Mainous 1975

Mandell 1974

Marx 1988

Marx 1990

Parmar 1998

Pavy 1995
Pavy JJ, Denekamp J, Letscher J, Litbrand B, Mornex F, Bernier J, et al. EORTC Late Effects Working Group. Late effects toxicity

**Rubin 1968**

**Rubin 1984**

**Schulz 1995**

**Stone 2003**

**Thompson 1999**

**Trott 1984**

**Waddell 1999**

**WHO 2004**

*Indicates the major publication for the study

## Tables

### Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Clarke 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Multicentre RCT with allocation concealment and patient/outcome assessor blinding.</td>
</tr>
<tr>
<td>Participants</td>
<td>68 patients with problematic radiation proctitis.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Control: Air breathing at 1ATA for 120 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 six to eight weeks</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Healing or significant improvement.</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hulshof 2002</td>
<td>Randomised trial using random number table with allocation concealment but no blinding. Randomised in matched pairs.</td>
<td>7 patients with cognitive deficits present at least 1.5 years after irradiation of the brain with at least 3000 cGy.</td>
<td>Control: Nil specific HBOT: 100% oxygen at 3 ATA for 115 minutes for 30 sessions over six weeks (five days out of seven each week).</td>
<td>Neuropsychiatric testing</td>
<td>Preliminary abstract report of one arm of 8 armed study</td>
</tr>
<tr>
<td>Marx 1985</td>
<td>Multicentre randomised trial. No details of methodology for randomisation, allocation concealment or blinding.</td>
<td>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.</td>
<td>Control: teeth extracted in standard way with 1 million units penicilling pre-extraction and 500mg four times each day for 10 days post-extraction. HBOT: 20 pre-operative treatment sessions at 2.4 ATA for 90 minutes daily five or six days each week, followed by 10 further sessions post-operatively.</td>
<td>Development of clinical osteoradionecrosis with non-healing at 6 months</td>
<td>Very low power study with many outcomes</td>
</tr>
<tr>
<td>Marx 1999a</td>
<td>Described as randomised. No details concerning blinding or allocation concealment.</td>
<td>104 patients requiring hemimandibular jaw reconstruction in tissue beds exposed to at least 6400 cGy radiotherapy. No other specific exclusions.</td>
<td>Control: Not stated HBOT: 20 pre-operative treatment sessions at 2.4 ATA for 90 minutes daily five days each week, followed by 10 further sessions post-operatively.</td>
<td>“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).</td>
<td>Sketchy account within a textbook chapter written by the author.</td>
</tr>
<tr>
<td>Marx 1999b</td>
<td>Described as randomised. No details concerning blinding or allocation concealment.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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Hyperbaric oxygen therapy for late radiation tissue injury (Review)  
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### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Participants</th>
<th>160 patients requiring major soft tissue surgery or flaps into an irradiated area (&gt;6,400 cGy). No other specific exclusions.</th>
</tr>
</thead>
</table>
| Interventions | Control: not stated  
HBOT: 20 pre-operative treatment sessions at 2.4 ATA for 90 minutes daily five days each week, followed by 10 further sessions post-operatively. |
| Outcomes | Wound infection, dehiscence, delayed healing |
| Notes | Sketchy account within a textbook chapter written by the author. |
| Allocation concealment | B |

#### Study  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. |
| Interventions | Control: 100 minutes at 2.4 ATA breathing 41% oxygen to simulate 100% oxygen at 1ATA, daily 5 days per week to a total of 30 sessions.  
HBOT: 100% oxygen breathing on the same schedule. |
| Outcomes | Sensory thresholds, quality of life scores, McGill pain Score, lymphoedema resolution |
| Notes | Many other outcomes reported |
| Allocation concealment | A |

**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-Grey  
**HBOT:** Hyperbaric oxygen therapy

### Characteristics of excluded studies

- **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 arms received some HBOT (1.2 versus 2.0 ATA)
**ADDITIONAL TABLES**

**Table 01. The LENT-SOMA Scales - Conceptual summary**

<table>
<thead>
<tr>
<th>Subjective</th>
<th>Objective</th>
<th>Medical management</th>
<th>Analytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>The injury from the patient point of view. May involve interview, diary or questionnaire depending on the system to be used.</td>
<td>Morbidity assessed objectively by clinician during physical examination.</td>
<td>The active steps that have been taken in order to ameliorate the symptoms.</td>
<td>Diagnostic and imaging tools used to further objectively define the level of injury.</td>
</tr>
</tbody>
</table>

**Table 02. Search Strategies**

**EMBASE**
1. exp radiation injury/
2. (head or neck or cerebr$ or cervi$ or brain$ or pelvi$ or mandib$ or chest or uter$ or bladder or bowel or rect$).mp.
3. (radiation$ or radiotherap$ or late$ or damag$ or wound$ or destruction$ or edema$ or edema$ or fracture$).mp.
4. 2 and 3
5. 1 or 4
6. exp radiotherapy/
7. 5 or 6
8. exp hyperbaric oxygen/
9. (high adj5 (pressur$ or oxygen$)).mp.
10. hyperbaric$.mp.
11. 8 or 9 or 10
12. oxygen$.mp.
13. 11 and 12
14. (HBO or HBOT).mp.
15. multiplace chamber$.mp.
16. monoplace chamber$.mp.
17. 13 or 14 or 15 or 16
18. 7 and 17
19. 18

**MEDLINE (OVID)**
1. exp radiation injuries
2. exp radiotherapy
3. head or neck or cervi$ or pelvi$ or mandib$ or chest or uter$ or bladder or bowel or rect$ or leg
4. radiation$ or radiation inj$ or late or damage$ or wound$ or destruction$ or oedema$ or edema$ or fracture$
5. 3 and 4
6. 1 or 2 or 5
7. exp hyperbaric oxygenation
8. (high*) adj3 (pressure or tension*)
9. hyperbaric*
10. oxygen*
11. 6 or 7 or 8
12. 9 and 10
13. HBO or HBOT
14. multiplace chamber*
15. monoplace chamber*
16. 11 or 12 or 13 or 14 or 15
17. 16 and 17

**GRAPHS**

**Comparison 02. Complete resolution of problem**

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Complete resolution of clinical problem at three months</td>
<td></td>
<td></td>
<td>Relative Risk (Random) 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>02 Sensitivity analysis for missing data in proctitis (best case)</td>
<td>1</td>
<td>68</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>3.33 [1.53, 7.26]</td>
</tr>
<tr>
<td>03 Sensitivity analysis for missing data in proctitis (worst case)</td>
<td>1</td>
<td>68</td>
<td>Relative Risk (Random) 95% CI</td>
<td>1.23 [0.71, 2.15]</td>
</tr>
</tbody>
</table>
### Comparison 03. Improvement in mean LENT-SOMA score

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LENT-SOMA score at three months</td>
<td>1</td>
<td>57</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>3.97 [1.69, 6.25]</td>
</tr>
</tbody>
</table>

### Comparison 04. Resolution of pain

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score change at end of treatment</td>
<td>1</td>
<td>34</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Pain score change at one year</td>
<td>1</td>
<td>34</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

### Comparison 05. Resolution of swelling

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of lymphoedema</td>
<td>1</td>
<td>34</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>5.00 [0.26, 97.00]</td>
</tr>
</tbody>
</table>

### Comparison 06. Improvements in quality of life or function

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 mean score at twelve months (general health)</td>
<td>1</td>
<td>34</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-2.30 [-18.95, 14.35]</td>
</tr>
<tr>
<td>SF-36 mean score for physical function at 12 months</td>
<td>1</td>
<td>34</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-4.00 [-19.40, 11.40]</td>
</tr>
</tbody>
</table>

### Comparison 07. Osteoradionecrosis

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete mucosal cover</td>
<td>2</td>
<td>178</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>1.38 [1.19, 1.61]</td>
</tr>
<tr>
<td>Establishment of bony continuity</td>
<td>1</td>
<td>104</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>1.41 [1.14, 1.75]</td>
</tr>
<tr>
<td>Successful healing of tooth sockets after tooth extraction</td>
<td>1</td>
<td>74</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>1.35 [1.08, 1.68]</td>
</tr>
</tbody>
</table>

### Comparison 11. Head and Neck

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound dehiscence</td>
<td>2</td>
<td>264</td>
<td>Relative Risk (Random) 95% CI</td>
<td>4.23 [1.06, 16.83]</td>
</tr>
</tbody>
</table>
### Comparison 12. Neurological tissue

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm sensory threshold one week after treatment (degrees Centigrade change from baseline)</td>
<td>1</td>
<td>34</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>1.12 [-1.90, 4.14]</td>
</tr>
<tr>
<td>Warm sensory threshold at one year</td>
<td>1</td>
<td>34</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-0.87 [-3.97, 2.23]</td>
</tr>
<tr>
<td>Net number of significantly improved neuropsychological tests at three months (25 tests total)</td>
<td>1</td>
<td>7</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>2.00 [-1.60, 5.60]</td>
</tr>
<tr>
<td>Net number of significantly improved neuropsychiatric tests at six months</td>
<td>1</td>
<td>7</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>1.00 [-3.55, 5.55]</td>
</tr>
</tbody>
</table>

---

### COVER SHEET

**Title**  
Hyperbaric oxygen therapy for late radiation tissue injury

**Authors**  
Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C

**Contribution of author(s)**  
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.

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Information not supplied by author

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Information not supplied by author

**Date authors’ conclusions section amended**  
Information not supplied by author

**Contact address**  
Dr Michael Bennett  
Medical Director
### Graphs and Other Tables

**Fig. 1.** Comparison 02. Complete resolution of problem

#### 02.01 Complete resolution of clinical problem at three months

**Review:** Hyperbaric oxygen therapy for late radiation tissue injury  
**Comparison:** 02 Complete resolution of problem  
**Outcome:** 01 Complete resolution of clinical problem at three months

<table>
<thead>
<tr>
<th>Study</th>
<th>HBOT n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Random) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Proctitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarke 2004</td>
<td>16/34</td>
<td>6/34</td>
<td></td>
<td>100.0</td>
<td>2.67 [1.19, 5.99]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>34</td>
<td></td>
<td></td>
<td>100.0</td>
<td>2.67 [1.19, 5.99]</td>
</tr>
<tr>
<td>Total events: 16 (HBOT), 6 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=2.38</td>
<td>p=0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Hemi-mandibular reconstruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marx 1999a</td>
<td>48/52</td>
<td>34/52</td>
<td></td>
<td>100.0</td>
<td>1.41 [1.14, 1.75]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>52</td>
<td></td>
<td></td>
<td>100.0</td>
<td>1.41 [1.14, 1.75]</td>
</tr>
<tr>
<td>Total events: 48 (HBOT), 34 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect z=3.18</td>
<td>p=0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03 Brachial plexus radiation neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>× Pritchard 2001</td>
<td>0/17</td>
<td>0/17</td>
<td></td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>17</td>
<td>17</td>
<td></td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

(Continued . . .)
### Study HBOT Control Relative Risk (Random) Weight Relative Risk (Random)
<table>
<thead>
<tr>
<th></th>
<th>n/N</th>
<th>n/N</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarke 2004</td>
<td>20/34</td>
<td>6/34</td>
<td>1.23 [ 0.71, 2.15 ]</td>
<td>100.0</td>
<td>1.23 [ 0.71, 2.15 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>34</td>
<td>34</td>
<td>100.0</td>
<td>3.33 [ 1.53, 7.26 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 16 (HBOT), 13 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: z=0.73 p=0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. Comparison 02. Complete resolution of problem

02.03 Sensitivity analysis for missing data in proctitis (worst case)

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 02 Complete resolution of problem
Outcome: 03 Sensitivity analysis for missing data in proctitis (worst case)
Fig. 4. Comparison 03. Improvement in mean LENT-SOMA score

**03.01 Mean LENT-SOMA score at three months**

<table>
<thead>
<tr>
<th>Study</th>
<th>HBOT N</th>
<th>Mean(SD)</th>
<th>Control N</th>
<th>Mean(SD)</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarke 2004</td>
<td>30</td>
<td>4.70 (4.70)</td>
<td>27</td>
<td>0.73 (4.10)</td>
<td>[ ]</td>
<td>100.0</td>
<td>[1.69, 6.25]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>30</td>
<td>27</td>
<td>[ ]</td>
<td>[ ]</td>
<td>100.0</td>
<td>[1.69, 6.25]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: z=3.41, p=0.0007

---

Fig. 5. Comparison 04. Resolution of pain

**04.01 Pain score change at end of treatment**

<table>
<thead>
<tr>
<th>Study</th>
<th>HBOT N</th>
<th>Mean(SD)</th>
<th>Control N</th>
<th>Mean(SD)</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pritchard 2001</td>
<td>17</td>
<td>5.30 (0.00)</td>
<td>17</td>
<td>1.20 (0.00)</td>
<td>[ ]</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17</td>
<td>17</td>
<td>[ ]</td>
<td>[ ]</td>
<td>0.0</td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: not applicable

---

Hyperbaric oxygen therapy for late radiation tissue injury (Review)

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Fig. 6. Comparison 04. Resolution of pain

04.02 Pain score change at one year

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 04 Resolution of pain
Outcome: 02 Pain score change at one year

<table>
<thead>
<tr>
<th>Study</th>
<th>HBOT N</th>
<th>Mean(SD)</th>
<th>Control N</th>
<th>Mean(SD)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pritchard 2001</td>
<td>17</td>
<td>-0.70 (0.00)</td>
<td>17</td>
<td>-5.00 (0.00)</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17</td>
<td></td>
<td>17</td>
<td></td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: not applicable

-10.0 -5.0 0 5.0 10.0
Favours HBOT Favours control

Fig. 7. Comparison 05. Resolution of swelling

05.01 Improvement of lymphoedema

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 05 Resolution of swelling
Outcome: 01 Improvement of lymphoedema

<table>
<thead>
<tr>
<th>Study</th>
<th>HBOT n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pritchard 2001</td>
<td>2/17</td>
<td>0/17</td>
<td>100.0</td>
<td>5.00</td>
<td>[0.26, 97.00]</td>
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<tr>
<td>Total (95% CI)</td>
<td>17</td>
<td>17</td>
<td>100.0</td>
<td>5.00</td>
<td>[0.26, 97.00]</td>
</tr>
</tbody>
</table>

Total events: 2 (HBOT), 0 (Control)
Test for heterogeneity: not applicable
Test for overall effect z=1.06  p=0.3

0.01 0.1 1 10 100
Favours control Favours HBOT
### Fig. 8. Comparison 06. Improvements in quality of life or function

06.01 SF-36 mean score at twelve months (general health)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean(SD)</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pritchard 2001</td>
<td>17</td>
<td>58.80 (23.90)</td>
<td>17</td>
<td>61.10 (25.60)</td>
<td>-2.30 (-18.95, 14.35)</td>
<td>100.0</td>
<td>-2.30 (-18.95, 14.35)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17</td>
<td>17</td>
<td></td>
<td></td>
<td>100.0 -2.30 [-18.95, 14.35]</td>
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<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect z=0.27  p=0.8

### Fig. 9. Comparison 06. Improvements in quality of life or function

06.02 SF-36 mean score for physical function at 12 months

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean(SD)</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pritchard 2001</td>
<td>17</td>
<td>53.50 (23.50)</td>
<td>17</td>
<td>57.50 (22.30)</td>
<td>-4.00 (-19.40, 11.40)</td>
<td>100.0</td>
<td>-4.00 (-19.40, 11.40)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17</td>
<td>17</td>
<td></td>
<td></td>
<td>100.0 -4.00 [-19.40, 11.40]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect z=0.51  p=0.6
### Fig. 10. Comparison 07. Osteoradionecrosis

07.01 Complete mucosal cover

**Review:** Hyperbaric oxygen therapy for late radiation tissue injury

**Comparison:** 07 Osteoradionecrosis

**Outcome:** 01 Complete mucosal cover

<table>
<thead>
<tr>
<th>Study</th>
<th>HBOT n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marx 1985</td>
<td>35/37</td>
<td>26/37</td>
<td></td>
<td>43.3</td>
<td>1.35 [1.08, 1.68]</td>
</tr>
<tr>
<td>Marx 1999a</td>
<td>48/52</td>
<td>34/52</td>
<td></td>
<td>56.7</td>
<td>1.41 [1.14, 1.75]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>89</td>
<td>89</td>
<td></td>
<td>100.0</td>
<td>1.38 [1.19, 1.61]</td>
</tr>
</tbody>
</table>

Total events: 83 (HBOT), 60 (Control)

Test for heterogeneity chi-square=0.09 df=1 p=0.76 I² =0.0%

Test for overall effect z=4.11 p=0.00004

Favours control Favours HBOT

### Fig. 11. Comparison 07. Osteoradionecrosis

07.02 Establishment of bony continuity

**Review:** Hyperbaric oxygen therapy for late radiation tissue injury

**Comparison:** 07 Osteoradionecrosis

**Outcome:** 02 Establishment of bony continuity

<table>
<thead>
<tr>
<th>Study</th>
<th>HBOT n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marx 1999a</td>
<td>48/52</td>
<td>34/52</td>
<td></td>
<td>100.0</td>
<td>1.41 [1.14, 1.75]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>52</td>
<td>52</td>
<td></td>
<td>100.0</td>
<td>1.41 [1.14, 1.75]</td>
</tr>
</tbody>
</table>

Total events: 48 (HBOT), 34 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=3.18 p=0.001

Favours control Favours HBOT
**Fig. 12. Comparison 07. Osteoradionecrosis**

**07.03 Successful healing of tooth sockets after tooth extraction**

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 07 Osteoradionecrosis
Outcome: 03 Successful healing of tooth sockets after tooth extraction

<table>
<thead>
<tr>
<th>Study</th>
<th>HBOT n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marx 1985</td>
<td>35/37</td>
<td>26/37</td>
<td>1.35 [1.08, 1.68]</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>37</td>
<td>37</td>
<td></td>
<td>100.0</td>
<td>1.35 [1.08, 1.68]</td>
</tr>
</tbody>
</table>

Test for overall effect $z=2.61$ $p=0.009$

**Fig. 13. Comparison 11. Head and Neck**

**11.01 Wound dehiscence**

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 11 Head and Neck
Outcome: 01 Wound dehiscence

<table>
<thead>
<tr>
<th>Study</th>
<th>Control n/N</th>
<th>HBOT n/N</th>
<th>Relative Risk (Random)</th>
<th>Weight (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Hemimandibular reconstruction (bone and soft tissue)</td>
<td>Marx 1999a</td>
<td>11/52</td>
<td>2.20 [0.82, 5.89]</td>
<td>52.4</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>52</td>
<td>2.20 [0.82, 5.89]</td>
<td>52.4</td>
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</tr>
<tr>
<td>Total events: 11</td>
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<td>52</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect $z=3.67$ $p=0.0002$

<table>
<thead>
<tr>
<th>Study</th>
<th>Control n/N</th>
<th>HBOT n/N</th>
<th>Relative Risk (Random)</th>
<th>Weight (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 Complex soft-tissue grafts/flaps</td>
<td>Marx 1999b</td>
<td>26/80</td>
<td>8.67 [2.73, 27.49]</td>
<td>47.6</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>80</td>
<td>8.67 [2.73, 27.49]</td>
<td>47.6</td>
<td></td>
</tr>
<tr>
<td>Total events: 26</td>
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<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect $z=2.04$ $p=0.04$
Fig. 14. Comparison 12. Neurological tissue

12.03 Warm sensory threshold one week after treatment (degrees Centigrade change from baseline)

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 12 Neurological tissue
Outcome: 03 Warm sensory threshold one week after treatment (degrees Centigrade change from baseline)

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>HBOT</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pritchard 2001</td>
<td>17</td>
<td>17</td>
<td>-0.12 (5.01)</td>
<td>100.0</td>
<td>1.12 [-1.90, 4.14]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17</td>
<td>17</td>
<td>100.0</td>
<td></td>
<td>1.12 [-1.90, 4.14]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect z=0.73 p=0.5

Fig. 15. Comparison 12. Neurological tissue

12.04 Warm sensory threshold at one year

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 12 Neurological tissue
Outcome: 04 Warm sensory threshold at one year

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>HBOT</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pritchard 2001</td>
<td>17</td>
<td>17</td>
<td>1.40 (5.54)</td>
<td>100.0</td>
<td>-0.87 [-3.97, 2.23]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17</td>
<td>17</td>
<td>100.0</td>
<td></td>
<td>-0.87 [-3.97, 2.23]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect z=0.55 p=0.6
Fig. 16. Comparison 12. Neurological tissue

12.06 Net number of significantly improved neuropsychological tests at three months (25 tests total)

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 12 Neurological tissue
Outcome: 06 Net number of significantly improved neuropsychological tests at three months (25 tests total)

<table>
<thead>
<tr>
<th>Study</th>
<th>HBOT N</th>
<th>Control N</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hulshof 2002</td>
<td>4</td>
<td>3</td>
<td>1.00 (3.40)</td>
<td>100.0</td>
<td>2.00 [-1.60, 5.60]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>4</td>
<td>3</td>
<td></td>
<td>100.0</td>
<td>2.00 [-1.60, 5.60]</td>
</tr>
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Test for heterogeneity: not applicable
Test for overall effect z=1.09 p=0.3

Fig. 17. Comparison 12. Neurological tissue

12.07 Net number of significantly improved neuropsychiatric tests at six months

Review: Hyperbaric oxygen therapy for late radiation tissue injury
Comparison: 12 Neurological tissue
Outcome: 07 Net number of significantly improved neuropsychiatric tests at six months

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<tr>
<th>Study</th>
<th>HBOT N</th>
<th>Control N</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
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</thead>
<tbody>
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<td>Hulshof 2002</td>
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<td>3</td>
<td>-1.00 (4.50)</td>
<td>100.0</td>
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<td>Total (95% CI)</td>
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<td>3</td>
<td></td>
<td>100.0</td>
<td>1.00 [-3.55, 5.55]</td>
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Test for heterogeneity: not applicable
Test for overall effect z=0.43 p=0.7