Hyperbaric oxygen therapy for promoting fracture healing and treating fracture non-union

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A substantive amendment to this systematic review was last made on 11 November 2004. Cochrane reviews are regularly checked and updated if necessary.

Abstract

Background: Hyperbaric oxygen therapy (HBOT) consists of intermittently administering 100% oxygen at pressures greater than one atmosphere absolute (ATA) in a pressure vessel. This technology has been used to treat a variety of diseases and has been described as helping patients who have delayed healing or established non-union of bony fractures.

Objective: The aim of this review was to assess the evidence for the benefit of hyperbaric oxygen treatment (HBOT) for the treatment of delayed bony healing and established non-union of bony fractures.

Search strategy: We searched the Cochrane Musculoskeletal Injuries Group trials register (to January week 3, 2004), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 4, 2003), MEDLINE (OVID 1966 to January week 3, 2004), CINAHL (OVID 1982 to January week 3, 2004), EMBASE (OVID 1980 to February 2004), the locally developed Database of Randomised Controlled Trials in Hyperbaric Medicine (available at www.hboevidence.com) from inception to March 2004, and reference lists of articles.

Selection criteria: We aimed to include all randomised controlled trials that compared the effect of HBOT with no HBOT (no treatment or sham).

Data collection and analysis: Two authors using standardised forms attempted to extract data independently.

Main results: No trials met the inclusion criteria. We excluded one trial that compared HBOT with no treatment because no clinical outcomes were reported.

Reviewers' conclusions: This systematic review failed to locate any relevant clinical evidence to support or refute the effectiveness of HBOT for the management of delayed union or established non-union of bony fractures. Good quality clinical trials are needed to define the role, if any, of HBOT in the treatment of these injuries.

Background

The treatment of fractures aims to re-establish the structural integrity of the fractured bone and thereby restore function to the injured body part. However, the fracture healing process is sometimes impaired leading to delayed or, in some cases, non-union of the fractured bone.

Non-union may be defined as an absent healing process after a duration of six months and is a major complication following skeletal trauma (Birnbaum 2002). Both delayed or non-union are usually associated with pain and reduced or loss of function. Rates vary widely with the clinical setting and fracture site. A review of mandibular fractures suggested a rate of 4.8%, while the rate following scaphoid fracture has been estimated at 10% (Hambidge 1999; Lamphier 2003).

Poor vascularity (poor/disrupted blood supply), infection, large gaps at the fracture site, unfavourable mechanical circumstances (poor fracture stability/stabilisation) and loss of soft tissues all hinder fracture healing. Non-union is often classified as hypervascular (hypertrophic) or avascular (atrophic) and may occur in the presence or absence of infection. Methods for treating delayed and non-union are multiple and often specific to a particular injury. They include bone grafting, internal and external fixation, extracorporeal shock wave therapy and electrical stimulation (Biedermann 2003; Gallay 2000; Simonis 2003). These treatments aim to close fracture gaps, provide stability and initiate osteogenesis (bone generation). Whilst it is conventional to stipulate a time limit for fracture healing, the real clinical issue is the potential for bone healing based on an assessment of the factors listed above. In cases where there is a strong possibility of a delayed or non-union, with serious consequences, extra interventions to promote healing are often appropriate. These may include interventions aimed at reducing other known risk factors for delayed healing, such as infection (Gosselin 2004) and smoking (Hoidrup 2000).

Hyperbaric oxygen therapy (HBOT) is an adjunctive therapy that has been proposed to improve outcome in delayed or non-union. HBOT is 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 administering 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased partial pressure of oxygen to the tissues. Typically, treatments involve pressurisation to between 1.5 and 3.0 ATA for periods between 60 and 120 minutes once or more daily.

It has been suggested since at least 1966 that HBOT might improve the outcome following bone fractures where delayed or non-healing is likely (Coulson 1966). In animal studies, HBOT has been shown to improve both bone generation (Coulson 1966; Inoue 2000; Tkachenko 1988) and the removal of dead or abnormal bone (Jones 1991; Strauss 1982). Benefits were less clear in a more recent study where cats with experimentally induced non-union showed increased bone formation but not improved vascularisation, radiologic appearance or histology (Kerwin 2000). There have been reports of clinical improvement following the application of HBOT to individuals with established non-union (Atesalp 2002), however, despite nearly 40 years of interest in the delivery of HBOT to patients with these problems, little comparative clinical evidence of effectiveness exists.

HBOT is associated with some risk of adverse effects including damage to the ears, sinuses and lungs from the effects of pressure (a problem lasting from one day to one or two weeks), temporary worsening of myopia (lasting several weeks) and claustrophobia (during therapy). Oxygen poisoning may manifest acutely as a neurologic event (often fitting but only a problem during therapy), or accumulate slowly over a protracted course of HBOT and manifest as a decrease in respiratory function (Kindwall 1999) (may last a few weeks). Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention.

Objectives

The aim of this review was to assess the evidence for the use of hyperbaric oxygen treatment (HBOT) as an adjunctive therapy for treating actual or expected delayed or non-union of bone fractures. Specifically we wanted to ask, does the addition of HBOT have an influence on:

- the proportion of such fractures that go on to heal?
- the rate of healing?
- pain?
- functional outcome?

In addition we intended to assess if HBOT is safe in the short and long term.

Criteria for considering studies for this review

Types of studies

We considered any randomised or quasi-randomised (use of a method of allocating participants to a treatment that is not strictly random; e.g. by date of birth or hospital record number) clinical trials that compared HBOT with no HBOT (no treatment or sham).

Types of participants

Any patient with a bony fracture.

Types of intervention

We accepted any standard HBOT regimen aimed at improving fracture healing or treating bony non-union. Generally, a standard regimen involves HBOT administered in a compression chamber between pressures of 1.5 ATA and 3.0 ATA and treatment times between 30 minutes and 120 minutes on at least one occasion. The comparator group was to be either no, or sham, HBOT. We would have accepted trials where any other therapy (e.g. internal fixation) was administered to both arms of the trial.

Types of outcome measures

Studies were eligible for inclusion if they reported any of the following outcome measures at any time:

- Primary outcomes
- (1) Number of trial participants achieving bony union. (We intended to discuss the definition of 'bony union' as defined in each trial.)
- (2) Time to achievement of bony union.

- Secondary outcomes
- (3) Pain.
- (4) Functional outcomes including patient rated activities of daily living.
- (5) Number of trial participants with malunion or cosmetic deformity.
- (6) Complications and adverse events e.g. those discussed in background.

Search strategy for identification of studies

See: Cochrane Bone, Joint and Muscle Trauma Group search strategy

We searched the Cochrane Musculoskeletal Injuries Group trials register (to January week 3, 2004), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 4, 2003), MEDLINE (1966 to January week 3, 2004), EMBASE (1980 to February week 1, 2004), CINAHL (1982 to January week 3, 2004) and a database developed in our hyperbaric facility, The Database of Randomised Trials in Hyperbaric Medicine (www.hboevidence.com/ accessed March 2004).

In MEDLINE (OVID WEB) a subject specific search strategy was combined with the optimum trial search strategy (Robinson 2002) (see Table 01) and modified for use in other databases. All languages were considered.

In addition we made a systematic search for relevant controlled trials in specific hyperbaric literature sources by:

- contacting experts in the field and leading hyperbaric therapy centres (as identified by personal communication and searching the Internet) and asking for additional relevant data in terms of published or unpublished randomised trials;
- handsearching relevant hyperbaric textbooks (Brubakk 2003; Jain 1999; Kindwall 1999; Oriani 1996), 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;
- contacting authors of relevant studies to request details of unpublished or ongoing investigations.

Methods of the review

- Trial retrieval and selection
- One reviewer (MB) was responsible for handsearching and the identification of eligible studies. Two reviewers (MB and RT) examined the electronic search results and identified studies for possible inclusion. Reports of these studies were retrieved in full and reviewed independently for inclusion by three reviewers, two of whom (MB, RT) have content expertise with HBOT and one (RS) with content expertise in orthopaedics. In addition, one of the reviewers (MB) has expertise in clinical epidemiology. No differences of opinion required resolution.

- Data extraction
- Reviewers attempted to extract data and trial details using a pre-piloted data extraction form developed for this review. No differences required resolution. Authors would have been contacted if there had been any ambiguity about the published data.

- Quality assessment
- We planned to assess study quality using an adaptation of the method outlined in Schulz 1995. Results from the study quality would have been presented in a descriptive manner. The characteristics to be assessed are outlined in Table 02.

- Data analysis
- Analyses were to be performed using the RevMan 4.2.3 software (RevMan 2003). We proposed to conduct intention-to-treat analyses wherever possible. Relative risks and 95 per cent confidence intervals were to be calculated for dichotomous outcomes, and mean differences and 95 per cent confidence intervals calculated for continuous outcomes. Results of comparable groups of trials were to be pooled using the fixed effects model and 95% confidence intervals. Heterogeneity between comparable trials would have been tested using the I2 statistic where required, and consideration given to the appropriateness of pooling.

Notes on decisions for pooling of outcome measures

- Primary outcomes
- (1) Proportion of participants achieving bony union (definition in each trial to be discussed and the appropriateness of pooling considered). Trials would have been pooled irrespective of the time of final follow-up. Where possible, the results would have been presented according to follow-up up to six months, between six and 12 months, and one year and above.

- (2) Time course to achieve union. This outcome may be presented as progress on X-Ray finding or clinical measure of stability. Pooling may be possible for comparable outcome measures.

- Secondary outcomes
- (3) Pain. We anticipated the use of visual analogue scales. Pooling would have been used when possible for comparable outcome measures.
- (4) Function. Compatible outcome measures enabling pooling are unlikely in trials testing union for different fracture sites. However, pooling may be undertaken where data are available for the proportion with a poor or worse functional outcome.
- (5) Malunion or cosmetic deformity. Pooling may be possible for comparable outcome measures in the future.
- (6) Complications and adverse events. Overall numbers of trial participants with complications or adverse effects would have been pooled if data were available.

- Sensitivity analyses
- Where appropriate, we planned sensitivity analyses investigating the effects of study quality (based on the Schulz quality score) and missing data. For the latter we would have conducted best and worst case analyses. The best-case scenario would assume 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 would be the reverse.

- Subgroup analysis
- Where appropriate data exists, we would consider subgroup analysis based on:
- (1) Indication for HBOT defined by extent of non-union at entry to studies (accelerated union versus delayed union versus established non-union).
- (2) Vascularity of problematic fracture (hypertrophic versus atrophic non-union).
- (3) Mode of fixation (internal/external/use of bone graft).
- (4) Use of exogenous bone growth factors or electrical field stimulators.
- (5) Nature of control group (sham versus no HBOT).
- (6) HBOT regimen: dose of oxygen received (pressure, time and length of treatment course).
- (7) Site of fracture (weightbearing versus non-weightbearing).

Tests of interaction would be calculated to determine if the results for subgroups are significantly different.

Description of studies

A total of 68 references were identified. Independent scrutiny of the titles and abstracts identified nine potentially relevant articles. After assessment of the full text, none of these articles met our inclusion criteria. Two gave animal data only (Ueng 1998; Ueng 1999), two dealt with serious vascular injuries in addition to fractures and were not randomised (Porcellini 1997; Zonis 1995), three were case series with no comparator group (Atesalp 2002; Braune 2002; Karapetian 1984) and one was a review containing no new data (Mathieu 1990). The final excluded study was an RCT of fracture healing that did not record any clinical outcome (Lindstromb 1998). See 'Characteristics of excluded studies' table for further details.

Methodological quality

There were no included studies for assessment.

Results

No trials met the inclusion criteria.

Discussion

This review failed to locate any randomised evidence to support or refute the treatment of fractures with hyperbaric oxygen therapy, whether to assist the management of complicated acute fractures, or to treat established non-union.

The only randomised trial in this area was Lindstromb 1998. This trial reported on 20 participants requiring intramedullary nailing for closed tibial fractures. The experimental group received 2.5 ATA 100% oxygen for 90 minutes daily for five days, and the outcomes measured were transcutaneous oxygen tension in the lower leg, limb temperature and blood flow in the tibialis posterior and dorsalis pedis arteries as assessed by doppler flow. Lindstrom reported some evidence of improved flow in the posterior tibial artery and in transcutaneous oxygenation in the HBOT group, and postulated these effects may have been secondary to reduced oedema. This trial did not report any clinical outcomes and the significance of these findings for fracture healing is not known.

Non-comparative studies suggest some potential benefit from HBOT, however the majority of these cases had multiple therapies instituted and it is not possible to ascribe a therapeutic effect to hyperbaric oxygen with any confidence.

Reviewers' conclusions

Implications for practice

There is insufficient evidence to support or refute the use of hyperbaric oxygen therapy for the treatment of fractures, whether to aid healing of acute injuries or as a therapy for established non-union.

Implications for research

Given the interest in HBOT for this difficult clinical problem, there is a case for achieving clinical trials of high methodological rigour specifically designed to assess the impact of HBOT in complex fractures and non-union. Specifically, information is required on the subset of fracture type or complexity most likely to benefit from this therapy, and the most appropriate oxygen dose.

Any future trials should be well reported, and consider in particular:

- appropriate sample sizes with power to detect expected differences
- careful definition and selection of target patients
- appropriate oxygen dose per treatment session (pressure and time)
- appropriate comparator therapy
- use of an effective sham therapy
- appropriate outcome measures including all those listed in this review
- careful elucidation of any adverse effects and their duration
- the cost-utility of the therapy

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and co-ordinating the comments for the final review, and Helen Handoll for her extensive editorial assistance. We would also like to thank the external referees for their constructive comments on the protocol (Mike Davies) and review (Phil Bryson).

Potential conflict of interest

None known

Tables

Characteristics of excluded studies

Study	Reason for exclusion
Atesalp 2002	Case series of non-union (14 subjects) - HBOT only used in two cases with re-infection.
Braune 2002	Case study of non-union treated with HBOT.
Karapetian 1984	Measured somatosensory potential in subjects with healing mandibular fracture - no comparator or clinical outcome. (Abstract only available).
Lindstrom 1998	RCT 20 subjects with tibial nailing. No clinical outcome reported.
Mathieu 1990	Review - no RCT data
Porcellini 1997	Case series (34 patients) with various vascular injuries and fracture. No comparator.
Ueng 1998	Animal data only. Effect of HBOT on healing after tibial lengthening in rabbits.
Ueng 1999	Animal data only. Effect of smoking and HBOT on bone healing in rabbits.
Zonis 1995	Case report in crush injury with fracture.

Additional tables

Table 01 Search strategy for MEDLINE (OVID WEB)

MEDLINE (OVID WEB)
1. exp Fractures/ 2. exp Fracture Fixation/ 3. Fracture Healing/ 4. fracture$.tw. 5. (delayed union or non union or nonunion or pseudarthos$).tw. 6. and/4-5 7. or/1-3,6 8. Hyperbaric Oxygenation/ 9. (high$ adj4 (pressure or tension$)).tw. 10. hyperbaric$ or barotherap$.tw. 11. or/9-10

12. oxygen$.tw.
13. and/11-12
14. (HBO or HBOT).tw.
15. ((monoplace or multiplace) adj chamber$).tw.
16. or/8,13-15
17. and/7,16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. Randomized Controlled Trials/
21. Random Allocation/
22. Double-Blind Method/
23. Single-Blind Method/
24. or/18-23
25. Animal/ not Human/
26. 24 not 25
27. clinical trial.pt.
28. exp Clinical Trials/
29. (clinic$ adj25 trial$).tw.
30. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
31. Placebos/
32. placebo$.tw.
33. random$.tw.
34. Research Design/
35. (latin adj square).tw.
36. or/27-35
37. 36 not 25
38. 37 not 26
39. Comparative Study/
40. exp Evaluation Studies/
41. Follow-Up Studies/
42. Prospective Studies/
43. (control$ or prospectiv$ or volunteer$).tw.
44. Cross-Over Studies/
45. or/39-44
46. 45 not 25
47. 46 not (26 or 38)
48. or/26,38,47
49. and/17,48

Table 02 Quality assessment criteria (Schulz 1995)

Randomisation	Allocation concealed	Selection bias	Masking
A = Adequate sequence generation is reported using random number tables, computer random number generator, coin tossing, or shuffling	A = Adequate measures to conceal allocations such as central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained convincing elements of concealment	A = Trials where an intention to treat analysis is possible and few losses to follow-up are noted	A = Double or triple blind
B = Did not specify one	B = Unclearly concealed	B = Trials which	B =

of the adequate reported methods in (A) but mentioned randomisation method	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)	reported exclusions (as listed in A but exclusions were less than 10%)	Single blind
C = Other methods of allocation that appear to be unbiased	C = Inadequately concealed trials in which method of allocation is not concealed such as alteration methods or use of case record numbers	C = No reporting on exclusions or exclusions greater than 10% or wide differences in exclusions between groups	C = Non-blind

References

** indicates the major publication for the study*

References to studies excluded from this review

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Cover sheet

Hyperbaric oxygen therapy for promoting fracture healing and treating fracture non-union

Reviewer(s)	Bennett MH, Stanford R, Turner R
Contribution of Reviewer(s)	MB conceived and designed the review, co-ordinated the contributions of the other authors, screened search results, appraised papers, was to have abstracted data, and wrote the review. MB is the guarantor of the review. RS co-authored the background and discussion, appraised papers, provided a clinical orthopaedic perspective and assessed recommendations from that viewpoint, and provided general editorial input. RT co-authored the background and discussion, appraised papers, was to have abstracted data and provided editorial input.

	Lesley Gillespie (Trials Search Co-ordinator, Cochrane Musculoskeletal Injuries Group) designed the search strategy.
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Date new studies found but not yet included/excluded	Information not supplied by reviewer
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Synopsis

Insufficient evidence to support or refute the use of hyperbaric oxygen therapy (HBOT) for fracture healing

Fractures are very common, and may fail to heal in a small percentage of cases with considerable loss of function and often continuing pain. HBOT aims to increase the supply of oxygen to the fracture site and improve healing. HBOT involves people breathing pure oxygen in a specially designed chamber (like those used for deep sea divers suffering pressure problems after resurfacing). This review found only one small randomised trial (RCT) which had no clinically important outcomes. There is, therefore, no evidence from RCTs to support the use of this treatment, which may, rarely, result in serious long-term adverse effects.

Keywords

Humans; *Fracture Healing; Fractures, Ununited[physiopathology][*therapy]; *Hyperbaric Oxygenation