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

Bennett MH, Stanford RE, Turner R

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 11

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

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

Michael H Bennett[1], Ralph E Stanford[2], Robert Turner[3]

[1]Department of Anaesthesia, Prince of Wales Hospital, Randwick, Australia. [2]Department of Orthopaedics, Prince of Wales Hospital, Randwick, Australia. [3]Department of Diving and Hyperbaric Medicine, Prince of Wales Hospital, Randwick, Australia

Contact address: Michael H Bennett, Department of Anaesthesia, Prince of Wales Hospital, Barker Street, Randwick, NSW, 2031, Australia. m.bennett@unsw.edu.au. s9400356@unsw.edu.au.

Editorial group: Cochrane Bone, Joint and Muscle Trauma Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 11, 2012.
Review content assessed as up-to-date: 17 July 2012.

Citation: Bennett MH, Stanford RE, Turner R. Hyperbaric oxygen therapy for promoting fracture healing and treating fracture non-union. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No.: CD004712. DOI: 10.1002/14651858.CD004712.pub4.

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. This is an update of a Cochrane Review first published in 2005, and previously updated in 2008.

Objectives

The aim of this review is 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 methods

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (July 2012), the Cochrane Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 7), MEDLINE (1946 to July Week 1 2012), EMBASE (1974 to 2012 July 16), CINAHL (1937 to 17 July 2012), the Database of Randomised Controlled Trials in Hyperbaric Medicine (accessed July 2012), the WHO International Clinical Trials Registry Platform (17 July 2012) and reference lists of articles.

Selection criteria

We aimed to include all randomised controlled trials comparing the clinical effects of HBOT with no HBOT (no treatment or sham) for healing of bony fractures and fracture non-unions.

Data collection and analysis

Two review authors independently screened electronic search results, and all three authors independently performed study selection. We planned independent data collection and risk of bias assessment by two authors using standardised forms.

Main results

No trials met the inclusion criteria. In this update, we identified three ongoing randomised controlled trials. Among the eight excluded studies were three randomised trials comparing HBOT with no treatment that included patients with fractures. One of these trials had been abandoned and the other two did not report on fracture healing outcomes.

Authors' 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. There are three randomised controlled trials underway and we anticipate these will help provide some relevant clinical evidence to address this issue in the future.

PLAIN LANGUAGE SUMMARY

Using oxygen at high pressure (in a compression chamber) for the treatment of broken bones

Broken bones (fractures) are very common and sometimes may take a long time to heal or in some cases may fail to heal. The resulting non-union can result in long-term pain and loss of function. The use of hyperbaric oxygen therapy (HBOT) has been suggested as a way to enhance healing and treat non-union. Hyperbaric oxygen therapy involves the delivery of oxygen at high pressure to patients in a specially designed chamber (like those used for deep sea divers suffering pressure problems after resurfacing). The aim is to increase the supply of oxygen to the fracture site, which theoretically should improve healing. It should be noted that hyperbaric oxygen therapy may, albeit rarely, result in serious long-term adverse effects.

This review found no evidence from randomised trials to support or refute the use of hyperbaric oxygen therapy to avoid or treat poorly healing broken bones. However, in this update, we found three ongoing randomised trials that are likely to provide some evidence to inform on the use of hyperbaric oxygen therapy in the future.

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 abnor-

mal 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 2008) (may last a few weeks). Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention.

This is an update of a Cochrane Review first published in 2005, and previously updated in 2008.

OBJECTIVES

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 whether the addition of HBOT has 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.

METHODS

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 or fracture non-union.

Types of interventions

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 the Background).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (July 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 7), MEDLINE (1946 to July Week 1 2012), EMBASE (1974 to 2012 July 16), CINAHL (1937 to 17 July 2012) and a database developed in our hyperbaric facility, The Database of Randomised Trials in Hyperbaric Medicine (accessed 20 July 2012).

In MEDLINE (Ovid) a subject specific search strategy was combined with the sensitivity-maximizing version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011) (*see* Appendix 1) and modified for use in *The Cochrane Library*, EMBASE and CINAHL (*see* Appendix 1). All languages were considered. Search strategies used for previous versions of this review are reported in Bennett 2005.
We searched the WHO International Clinical Trials Registry Platform for ongoing or recently completed trials (17 July 2012) (search terms: hyperbaric and oxygen and fracture*).

Searching other resources

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

- handsearching relevant hyperbaric textbooks (Brubakk 2003; Jain 2009; Kindwall 2008; Mathieu 2006), journals (Undersea and Baromedical Research 1974-1992; Undersea and Hyperbaric Medicine 1993 to June 2012; Hyperbaric Oxygen Review 1980 to 1985; South Pacific Underwater Medicine Society (SPUMS) Journal 1975 to 2007; Diving and Hyperbaric Medicine 2007 to June 2012, European Journal of Hyperbaric Medicine 2000 to 2007 and Aviation, Space and Environmental Medicine Journal 2000 to June 2012) and conference proceedings (Undersea and Hyperbaric Medical Society 1980 to 2012; SPUMS 1992 to 2012, European Undersea and Baromedical Society 1996 to 2011, International Congress of Hyperbaric Medicine 1980 to 2011).
- contacting authors of relevant studies to request details of unpublished or ongoing investigations.

For the previous version of our review (Bennett 2005), we contacted experts in the field and leading hyperbaric therapy centres (as identified by personal communication and searching the Internet) and asked for additional relevant data in terms of published or unpublished randomised trials.

Data collection and analysis

Selection of studies

One review author (MB) was responsible for handsearching and the identification of eligible studies. Two review authors (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 review authors, two of whom (MB and RT) have content expertise in HBOT and one (RS) in orthopaedics. In addition, one of the review authors (MB) has expertise in clinical epidemiology. No differences of opinion required resolution.

Data extraction and management

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

Assessment of risk of bias in included studies

We planned to assess study quality using the risk of bias tool as recommended in the Cochrane Handbook (Higgins 2011). This table assesses the risk of bias for each study across seven domains: sequence generation, allocation concealment, blinding (of participants and care providers), blinding (of outcome assessors), incomplete outcome data, selective outcome reporting and a miscellaneous domain for any other source of bias.

Data synthesis

Analyses were to be performed using the RevMan software (RevMan 2011). We proposed to conduct intention-to-treat analyses wherever possible. Risk ratios and 95% confidence intervals were to be calculated for dichotomous outcomes, and mean differences and 95% confidence intervals calculated for continuous outcomes. Results of comparable groups of trials were to be pooled using the fixed-effect model and 95% confidence intervals. Heterogeneity between comparable trials would have been tested using the I^2 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.

Subgroup analysis and investigation of heterogeneity

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.

Sensitivity analysis

Where appropriate, we planned sensitivity analyses investigating the effects of including data from trials at high or unclear risk of selection bias (lack of allocation concealment) and detection bias (lack of assessor blinding) 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.

RESULTS

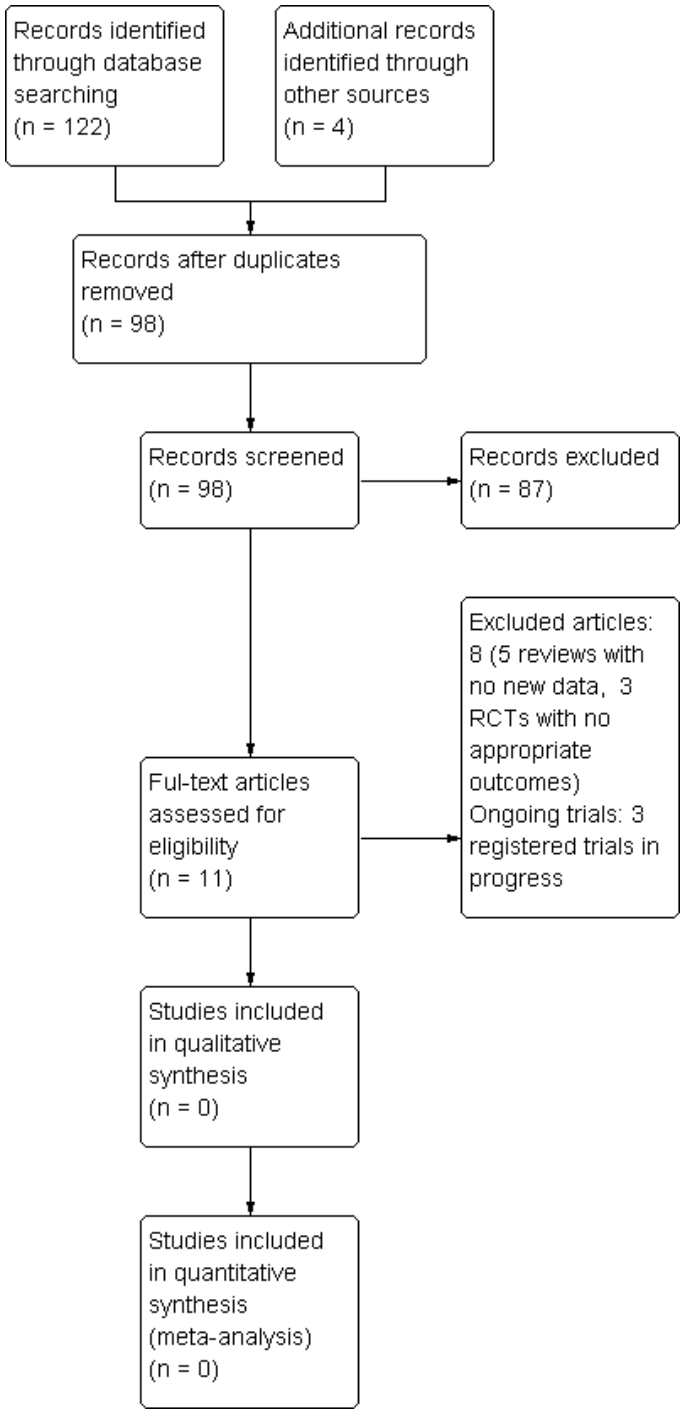
Description of studies

See: Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

For this update, completed July 2012, we screened a total of 122 records from the following databases: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (5 records); Cochrane Central Register of Controlled Trials (8), MEDLINE (17), EMBASE (41), CINAHL (48), the Database of Randomised Trials in Hyperbaric Medicine (0), and the WHO International Clinical Trials Registry Platform (3). Four potentially relevant publications were forwarded to us by colleagues; all had been identified by our electronic search strategy. Figure 1 shows the study flow diagram.

Figure 1. Study selection flow diagram.



The full search resulted in the identification of 11 potentially eligible studies, for which (where possible) full reports were obtained. Upon study selection, none were included, eight were excluded (Barata 2011; Bouachour 1996; Buettner 2007; Karamitros 2006; Lindstrom 1998; Mathieu 1990; Wang 2002; Williamson 2006), and three are ongoing studies (NCT00264511; NCT01264146; NCT01365780). A reappraisal of the nine excluded studies included in the previous version of the review resulted in the complete removal of seven clearly non-eligible studies.

Overall, there are no included trials, eight excluded studies and three ongoing trials.

Among the currently listed excluded studies, three were randomised trials of crush injuries in the lower leg, but none reported any outcomes relevant to fracture healing or non-union (Bouachour 1996; Lindstrom 1998; Williamson 2006). See the Characteristics of excluded studies for further details.

Further details of the ongoing studies (NCT00264511 (also registered in India as CTRI/2010/091/000369)); NCT01264146; NCT01365780 (not yet recruiting)) are presented in the Characteristics of ongoing studies.

The results from the previous search (up to April 2008) are shown in Appendix 2.

Risk of bias in included studies

There were no included studies for assessment.

Effects of interventions

No trials met the inclusion criteria.

DISCUSSION

Summary of main results

This review failed to locate any randomised trial 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. Three trials are registered in this area and may provide relevant data in the future (*see* Characteristics of ongoing studies). The 'Hyperbaric Oxygen for Lower Limb Trauma' (HOLLT) study is a multinational, non-blinded, randomised trial enrolling patients with crush injuries where there is a complex fracture of the lower leg (NCT00264511). Patients are randomised to a standard surgical protocol or the same protocol with adjunctive HBOT in the acute phase. The HOCIF trial is designed to assess complication rates after plating of calcaneal fractures and it is not clear if outcomes relevant to this review will be measured (NCT01264146). Finally, the same primary investigator of the HOCIF trial is planning a similar study (HBOTRadius) of distal radius fracture requiring surgical plating (NCT01365780). The recruitment status of this trial is unknown. These three trials aim to recruit 250, 160 and 100 participants respectively.

Overall completeness and applicability of evidence

While we believe we have located all the relevant human trials studying HBOT in bone fractures, the evidence that HBOT has a positive influence is anecdotal. There are three published randomised controlled trials in this area, but none provided data relevant to this review (Bouachour 1996; Lindstrom 1998; Williamson 2006). Bouachour 1996 enrolled 36 patients with crush injuries, 26 of whom had fractures, but measured only soft-tissue outcomes. This trial is included in the Cochrane Review on HBOT for treating acute surgical and traumatic wounds (Eskes 2010). Lindstrom 1998 enrolled 20 patients requiring intramedullary nailing for closed tibial fractures, but did not report on fracture healing. This trial did report 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. The significance of these findings for fracture healing is not known. Williamson 2006 is a brief report of a randomised trial involving patients with severe open tibial fractures (Gustillo 3B,3C) treated with or without HBOT. It was abandoned after 17 patients and though the patients were followed up, no outcome data were available in the abstract report of this trial. This group is now the primary research centre for the ongoing HOLLT study discussed above.

Agreements and disagreements with other studies or reviews

We have located a number of reviews, the most recent of which was published in 2011 (Barata 2011; Buettner 2007; Karamitros 2006; Wang 2002). In general, there is agreement that more work is needed in order to establish or refute the place of HBOT in the treatment of bony fractures, although some of these authors support the use of HBOT on mechanistic grounds and uncontrolled series (Karamitros 2006; Wang 2002). Buettner 2007 describes the level of evidence as high in the setting of crush injury and routine treatment as justified. There has been little work specifically on the treatment of fracture non-union.

AUTHORS' 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. Further evidence should be generated from trials that are ongoing at the time of writing.

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. Three trials are underway and there are indications that many of the trial characteristics, identified previously (Bennett 2005), will be satisfied in at least one of these trials. Where possible, we have indicated which of these characteristics are likely to be met. All the trials have carefully selected inclusion criteria designed to enrol patients with a specific fracture in order to reduce the possibility of selection bias between groups.

Desirable characteristics of future trials, and an indication if these are likely to be met by the trials underway:

- appropriate sample sizes with power to detect expected differences (yes - HOLLT (NCT00264511))
- careful definition and selection of target patients (yes - all trials)
- appropriate oxygen dose per treatment session (pressure and time) (yes - all trials)
- appropriate comparator therapy (yes - all trials)
- use of an effective sham therapy (no - none are sham trials)
- appropriate outcome measures including all those listed in this review (yes - HOLLT)
- careful elucidation of any adverse effects and their duration (yes - HOLLT)
- the cost-utility of the therapy (no)

All trials should be well reported using the CONSORT guidelines for randomised trials.

ACKNOWLEDGEMENTS

The authors acknowledge the support and extensive editorial feedback from Helen Handoll. We are also grateful to Joanne Elliott, Lindsey Elstub and the editors of the Cochrane Bone, Joint and Muscle Trauma Group for their assistance in the preparation of versions of this review.

In particular, we acknowledge the help of Lesley Gillespie with developing the original search strategy and Kate Rowntree for co-ordinating the comments for the first version of the review. We would also like to thank the external referees for their constructive comments on the protocol (Mike Davis) and review (Phil Bryson).

REFERENCES

References to studies excluded from this review

Barata 2011 *{published data only}*
Barata P, Cervaens M, Resende R, Camacho O, Marques F. Hyperbaric oxygen effects on sports injuries. *Therapeutic Advances in Musculoskeletal Disease* 2011;**3**(2):111–21.

Bouachour 1996 *{published data only}*
Bouachour G, Cronier P, Gouello JP, Toulemonde JL, Talha A, Alquier P. Hyperbaric oxygen therapy in the management of crush injuries: a randomized double-blind placebo-controlled clinical trial. Journal of Trauma 1996; Vol. 41, issue 2:333–9. [: CN–00128178]

Buettner 2007 *{published data only}*
Beuttner MF, Wolkenhauer D. Hyperbaric oxygen therapy in the treatment of open fractures and crush injuries. *Emergency Medicine Clinics Of North America* 2007;**25**(1): 177–88.

Karamitros 2006 *{published data only}*
Karamitros AE, Kalentzos VN, Soucacos PN. Electric stimulation and hyperbaric oxygen therapy in the treatment of nonunions. *Injury* 2006;**37(Suppl 1)**:s63–73.

Lindstrom 1998 *{published data only}*
* Lindstrom T, Gullichsen E, Lertola K, Niinikoski J. Effects of hyperbaric oxygen therapy on perfusion parameters and transcutaneous oxygen measurements in patients with intramedullary nailed tibial shaft fractures. *Undersea & Hyperbaric Medicine* 1998;**25**(2):87–91.
Lindstrom T, Gullichsen E, Niinikoski J. Effects of hyperbaric oxygen therapy (HBOT) on soft tissue perfusion in patients with intramedullary nailed tibial shaft fractures. *Annales Chirurgiae et Gynaecologiae* 1999;**88**(2):159.

Mathieu 1990 *{published data only}*
Mathieu D, Wattel F. Value of hyperbaric oxygen therapy in the treatment of post-traumatic osteitis [Interet de l'oxygenotherapie hyperbare dans le traitement des osteites posttraumatiques]. *Helvetica Chirurgica Acta* 1990;**56**(6): 865–78.

Wang 2002 *{published data only}*
Wang J, Li F, Calhoun JH, Mader JT. The role and

effectiveness of adjunctive hyperbaric oxygen therapy in the management of musculoskeletal disorders. *Journal of Postgraduate Medicine* 2002;**48**(3):226–31.

Williamson 2006 ***{published data only}***
Williamson OD, Millar I, Venturoni C. Hyperbaric oxygen and the management of open tibial fractures [abstract]. Journal of Bone and Joint Surgery - British Volume 2006; Vol. 88, issue Suppl 2:323. [: CN–00600758]

References to ongoing studies

NCT00264511 ***{unpublished data only}***
* Millar IL. Hyperbaric oxygen in lower leg trauma. http://clinicaltrials.gov/show/NCT00264511 (accessed 17 January 2012).
Sahni T. Hyperbaric Oxygen in Lower Limb Trauma (HOLLT) - An international, multicentre, randomized controlled study. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=1570 (accessed 17 January 2012). [: Registered as CTRI/2010/091/000369 in India]

NCT01264146 ***{unpublished data only}***
Knobe M, Moji SC. Hyperbaric oxygen therapy in calcaneal intraarticular fractures: can it decrease the soft-tissue complication rate? (HOCIF). http://clinicaltrials.gov/show/NCT01264146 (accessed 17 January 2012).

NCT01365780 ***{unpublished data only}***
Knobe M, Pape H-C. Hyperbaric oxygen therapy in distal radius fractures: can it shorten recovery time and increase fracture healing? HBOTRadius. http://clinicaltrials.gov/show/NCT01365780 (accessed 17 January 2012).

Additional references

Atesalp 2002
Atesalp AS, Komurcu M, Basbozkurt M, Kurklu M. The treatment of infected tibial nonunion with aggressive debridement and internal bone transport. *Military Medicine* 2002;**167**:978–81.

Biedermann 2003
Biedermann R, Martin A, Handle G, Auckenthaler T, Bach C, Krismer M. Extracorporeal shock waves in the treatment of nonunions. *Journal of Trauma* 2003;**54**(5):936–42.

Birnbaum 2002
Birnbaum K, Wirtz DC, Siebert CH, Heller KD. Use of extracorporeal shock-wave therapy (ESWT) in the treatment of non-unions. A review of the literature. *Archives of Orthopaedic Trauma Surgery* 2002;**122**(6):324–30.

Brubakk 2003
Brubakk AO, Neuman TS, editor(s). *Bennett and Elliott's physiology and medicine of diving*. 5th Edition. London: Saunders, 2003.

Coulson 1966
Coulson DB, Ferguson AB Jr, Diehl RC Jr. Effect of hyperbaric oxygen on the healing femur of the rat. *Surgical Forum* 1966;**17**:449–50.

Eskes 2010
Eskes A, Ubbink DT, Lubbers M, Lucas C, Vermeulen H. Hyperbaric oxygen therapy for treating acute surgical and traumatic wounds. *Cochrane Database of Systematic Reviews* 2010, Issue 10. [DOI: 10.1002/14651858.CD008059.pub2]

Gallay 2000
Gallay SH, McKee MD. Operative treatment of nonunions about the elbow. *Clinical Orthopaedics and Related Research* 2000;**(370)**:87–101.

Gosselin 2004
Gosselin RA, Roberts I, Gillespie WJ. Antibiotics for preventing infection in open limb fractures. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD003764.pub2]

Hambidge 1999
Hambidge JE, Desai VV, Schranz PJ, Compson JP, Davis TR, Barton NJ. Acute fractures of the scaphoid. Treatment by cast immobilisation with the wrist in flexion or extension? . *Journal of Bone and Joint Surgery. British Volume* 1999;**81**(1):91–2.

Higgins 2011
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8.5: The Cochrane Collaboration's tool for assessing risk of bias. In: Higgins JPT, Green S (editors). Cochrane Handbook of Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoidrup 2000
Hoidrup S, Prescott E, Sorensen TI, Gottschau A, Lauritzen JB, Schroll M, et al.Tobacco smoking and risk of hip fracture in men and women. *International Journal of Epidemiology* 2000;**29**(2):253–9.

Inoue 2000
Inoue O, Isa S, Nohara A, Sunagawa M, Okuda Y. Bone histomorphometric study on callus formation under hyperbaric oxygenation at osteotomised tibia in the dog [abstract]. *Undersea and Hyperbaric Medicine* 2000;**27**(Suppl):36.

Jain 2009
Jain KK. *Textbook of hyperbaric medicine*. 5th Edition. Cambridge, MA: Hogrefe Publishing, 2009.

Jones 1991
Jones JP, Lewis RH, Lewis T, Faugere MC, Malluch HH. The effect of hyperbaric oxygen on osteonecrosis [abstract]. *Orthopaedic Transactions* 1991;**15**:588.

Kerwin 2000
Kerwin SC, Lewis DD, Elkins AD, Oliver JL, Hosgood G, Pechman RD Jr, et al.Effect of hyperbaric oxygen treatment on incorporation of an autogenous cancellous bone graft in a nonunion diaphyseal ulnar defect in cats. *American Journal of Veterinary Research* 2000;**61**(6):691–8.

Kindwall 2008
Kindwall EP, Whelan HT, editor(s). *Hyperbaric medicine practice*. 3rd Edition. Flagstaff, AZ: Best Publishing Company, 2008.

Lamphier 2003
Lamphier J, Ziccardi V, Ruvo A, Janel M. Complications of mandibular fractures in an urban teaching center. *Journal of Oral and Maxillofacial Surgery* 2003;**61**(7):745–9.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6.4.11: Search filters. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Mathieu 2006
Mathieu D, Editor. *Handbook on hyperbaric medicine*. 2nd Edition. Berlin: Springer, 2006.

RevMan 2011
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Simonis 2003
Simonis RB, Parnell EJ, Ray PS, Peacock JL. Electrical treatment of tibial non-union: a prospective, randomised, double-blind trial. *Injury* 2003;**34**(5):357–62.

Strauss 1982
Strauss MB, Malluche HH, Faugere MC, Greenberg DA, Hart GB, Green S. Effect of hyperbaric oxygen on bone resorption in rabbits. Seventh Annual Conference of the Clinical Applications of Hyperbaric Oxygen; 1982 June 9 11; Anaheim (CA). 1982.

Tkachenko 1988
Tkachenko SS, Rutskii VV, Tikhilov RM, Vovchenko VI. Normalization of bone regeneration by oxygen barotherapy [Normalizatsiia osteoreparatsii vozdeistveim oksigenobaroterapii]. *Vestnik Khirurgii Imeni i - i - Grekova* 1988;**140**(3):97–100.

References to other published versions of this review

Bennett 2005
Bennett MH, Stanford RE, Turner R. Hyperbaric oxygen therapy for promoting fracture healing and treating fracture non-union. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD004712.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Barata 2011	Review only, no new data.
Bouachour 1996	An RCT of HBOT involving 36 patients with crush injuries, 26 of whom had fractures. The focus was on traumatic soft-tissue injury. The trial is reported in a Cochrane Review on HBOT for acute surgical and traumatic wounds (Eskes 2010).
Buettner 2007	Review only, no new data.
Karamitros 2006	Review only, no new data.
Lindstrom 1998	RCT involving 20 participants with intramedullary nailing of tibial shaft fractures. No clinical outcome reported
Mathieu 1990	Review - no RCT data.
Wang 2002	Review only, no new data.
Williamson 2006	An RCT of HBOT involving patients with severe open tibial fractures (Gustillo 3B,3C). This was abandoned after 17 patients and, though the patients were followed up, no outcome data were available in the abstract report of this trial Experience with this trial led to an international collaboration for a multi-centre RCT (*see* ongoing trial NCT00264511).

HBOT = hyperbaric oxygen therapy
RCT = randomised controlled trial

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

NCT00264511

Trial name or title	"Does hyperbaric oxygen reduce complications and improve outcomes after open tibial fractures with severe soft tissue injury? An international multi-centre randomized controlled trial."
Methods	Multi-centre international randomised controlled trial
Participants	Estimated enrolment: 250 people with acute fracture of the tibia with significant soft tissue injury of Gustilo Grade 3; enrolment within 48 hours of injury with expectation of commencement of HBO therapy within 48 hours of injury, valid consent
Interventions	Hyperbaric oxygenation versus control

NCT00264511 (*Continued*)

Outcomes	Primary outcome measures: acute phase complication rate; soft tissue necrosis; acute infection; compartment syndrome Secondary outcome measures: amputation rate; late infection; radiological union; quality of life score; functional outcome scores
Starting date	February 2006
Contact information	Ian L Millar, I.millar@alfred.org.au Hyperbaric Service, The Alfred Hospital, PO BOX 315, Melbourne, Victoria 3004, Australia
Notes	Estimated study completion date: June 2012 This trial is also registered in India under a separate identifier: CTRI/2010/091/000369

NCT01264146

Trial name or title	"Hyperbaric oxygen therapy in calcaneal intraarticular fractures: can it decrease the soft-tissue complication rate? (HOCIF)"
Methods	Randomised controlled trial (single centre)
Participants	Estimated enrolment: 160 people who have open reduction and internal fixation of an acute displaced intraarticular calcaneal fracture; aged 18 years or older
Interventions	Hyperbaric oxygen therapy 20 postoperative days (one time, 90 minutes a day) versus placebo (sham) control
Outcomes	Primary outcome measure: postoperative rate of wound complication after calcaneal plating [time frame 30 days] Secondary outcome measure: postoperative microcirculation of the foot, clinical outcome [time frame 2 years]
Starting date	January 2011
Contact information	Matthias Knobe: mknobe@ukaachen.de Saskia C Mooij: smooij@ukaachen.de Department of Orthopedic Trauma, RWTH Aachen University, Aachen, Germany
Notes	Estimated study completion date: July 2014 It is possible that this trial may not collect our listed outcomes

NCT01365780

Trial name or title	"Hyperbaric oxygen therapy in distal radius fractures: can it shorten recovery time and increase fracture healing? (HBOTRadius)"
Methods	Open label RCT
Participants	Estimated enrolment: 100 adult patients with distal radius fracture requiring surgical plating

NCT01365780 (*Continued*)

Interventions	Usual care versus usual care with 10 sessions of hyperbaric oxygen therapy
Outcomes	Primary outcome Primary outcome measures: functional outcome [time frame: 18 months] "The functional outcome is measured by microcirculation as parameter for wound healing, force of the treated hand and level of pain."
Starting date	Not yet enrolling*
Contact information	Matthias Knobe, MD mknobe@ukaachen.de Department of Orthopedic Trauma, RWTH Aachen University, Aachen, Germany
Notes	* Information on status last updated in July 2011.

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (Wiley Online Library)

#1 MeSH descriptor Fractures, Bone explode all trees (3390)
#2 MeSH descriptor Fracture Fixation explode all trees (992)
#3 MeSH descriptor Fracture Healing, this term only (327)
#4 fracture*:ti,ab,kw (7097)
#5 (delayed union or non union or nonunion or pseudarthos*):ti,ab,kw (334)
#6 (#1 OR #2 OR #3 OR #4 OR #5) (7215)
#7 MeSH descriptor Hyperbaric Oxygenation, this term only (331)
#8 (high* NEAR/4 (pressure or tension*)):ti,ab,kw (5751)
#9 (hyperbaric* or barotherap*):ti,ab,kw (1406)
#10 (#8 OR #9) (7133)
#11 (oxygen*):ti,ab,kw (20763)
#12 (#10 AND #11) (1121)
#13 (HBO or HBOT):ti,ab,kw (163)
#14 (monoplace or multiplace) NEAR chamber*:ti,ab,kw (19)
#15 (#7 OR #12 OR #13 OR #14) (1136)
#16 (#6 AND #15) (8)

MEDLINE (Ovid)

1 exp Fractures, Bone/ (129394)
2 exp Fracture Fixation/ (43536)
3 Fracture Healing/ (8232)
4 fracture$.tw. (145138)
5 (delayed union or non union or nonunion or pseudarthos$).tw. (7672)
6 and/4-5 (5058)
7 or/1-3,6 (137857)
8 Hyperbaric Oxygenation/ (9597)
9 (high$ adj4 (pressure or tension$)).tw. (53643)
10 (hyperbaric$ or barotherap$).tw. (9827)
11 or/9-10 (63137)
12 oxygen$.tw. (301005)
13 and/11-12 (10963)
14 (HBO or HBOT).tw. (2114)
15 ((monoplace or multiplace) adj chamber$).tw. (58)
16 or/8,13-15 (14520)
17 and/7,16 (137)
18 Randomized controlled trial.pt. (331546)
19 Controlled clinical trial.pt. (84599)
20 randomized.ab. (234978)

21 placebo.ab. (132769)
22 Drug Therapy.fs. (1549547)
23 randomly.ab. (169285)
24 trial.ab. (243449)
25 groups.ab. (1111291)
26 or/18-25 (2879437)
27 exp Animals/ not Humans/ (3752922)
28 26 not 27 (2445408)
29 17 and 28 (17)

EMBASE (Ovid)

1 exp Fracture/ (184351)
2 Fracture Fixation/ (20111)
3 fracture$.tw. (185902)
4 (delayed union or non union or nonunion or pseudarthos$).tw. (9327)
5 or/1-4 (246114)
6 Hyperbaric Oxygenation/ (13263)
7 (high* adj4 (pressure or tension*)).tw. (71497)
8 (hyperbaric* or barotherap*).tw. (12841)
9 or/7-8 (83897)
10 oxygen*.tw. (391682)
11 and/9-10 (14119)
12 (HBO or HBOT).tw. (2544)
13 ((monoplace or multiplace) adj chamber$).tw. (64)
14 or/6,11-13 (19394)
15 and/5,14 (280)
16 Randomized Controlled Trial/ (327549)
17 Clinical Trial/ (872756)
18 Controlled Clinical Trial/ (390330)
19 Randomization/ (58833)
20 Single Blind Procedure/ (16108)
21 Double Blind Procedure/ (112190)
22 Crossover Procedure/ (34409)
23 Placebo/ (214085)
24 Prospective Study/ (208388)
25 ((clinical or controlled or comparative or placebo or prospective$ or randomi#ed) adj3 (trial or study)).tw. (653899)
26 (random$ adj7 (allocat$ or allot$ or assign$ or basis$ or divid$ or order$)).tw. (156393)
27 ((singl$ or doubl$ or trebl$ or tripl$) adj7 (blind$ or mask$)).tw. (151978)
28 (cross?over$ or (cross adj1 over$)).tw. (64346)
29 ((allocat$ or allot$ or assign$ or divid$) adj3 (condition$ or experiment$ or intervention$ or treatment$ or therap$ or control$ or group$)).tw. (197742)
30 RCT.tw. (9639)
31 or/16-30 (1730904)
32 Case Study/ or Abstract Report/ or Letter/ (872075)
33 31 not 32 (1694818)
34 15 and 33 (41)

CINAHL (EBSCOhost)

S1 (MH “Fractures+”) (26080)
S2 (MH “Fracture Fixation”) (5212)
S3 (MH “Fracture Healing”) (1745)

S4 TX fracture* (35599)
S5 TX delayed union or non union or nonunion or pseudarthos* (1500)
S6 S1 or S2 or S3 or S4 or S5 (36124)
S7 (MH "Hyperbaric Oxygenation") (1330)
S8 TX (high* n4 pressure) or (high n4 tension*) (9494)
S9 TX hyperbaric* or barotherap* (1800)
S10 S8 or S9 (11264)
S11 TX oxygen* (35074)
S12 S10 and S11 (2049)
S13 TX HBO or HBOT (335)
S14 TX (monoplace or multiplace) n1 chamber* (11)
S15 S7 or S12 or S13 or S14 (2132)
S16 S6 and S15 (48)

Appendix 2. Previous results of search (Bennett 2005)

Description of studies

No new trials were identified on updating the search from January 2004 to April 2008.
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 randomised controlled trial (RCT) of fracture healing that did not record any clinical outcome (Lindstrom 1998).
Note that only Lindstrom 1998 and Mathieu 1990 were retained as excluded studies in the 2012 update.

WHAT'S NEW

Last assessed as up-to-date: 17 July 2012.

Date	Event	Description
2 October 2012	New search has been performed	For this update, published in Issue 11, 2012, the following changes were made: 1. The search strategies were revised and updated. 2. The search was updated to July 2012. 3. No new studies were included, six new studies were excluded and three ongoing studies were newly identified. 4. A reappraisal of the eligibility of nine previously excluded studies resulted in the deletion of seven non-eligible studies. 5. As per Collaboration guidance, the methods were updated to assess risk of bias
2 October 2012	New citation required and conclusions have changed	The 'Implications for research' section has been changed in light of three newly-identified ongoing studies

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 1, 2005

Date	Event	Description
5 May 2011	Amended	Converted to new review format.
3 June 2008	New search has been performed	Review updated June 2008. Updated search 20 April 2008. 'Synopsis' converted to 'Plain language summary'

CONTRIBUTIONS OF AUTHORS

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.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- South Eastern Sydney Area Health Service, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Should we locate studies for inclusion, we now plan to make a risk of bias assessment using the risk of bias table as recommended in the Cochrane Handbook (see methods).

2. The following changes were made to the search strategies in the 2012 update:

- We revised the search strategies to broaden the search.
- The MEDLINE strategy used the latest Cochrane Highly Sensitive Search Strategy for identifying randomised trials.
- The CINAHL search strategy was run using EBSCOhost.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans