Recompression and adjunctive therapy for decompression illness

Review information

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Citation example: Bennett MH, Lehm JP, Mitchell SJ, Wasiak J. Recompression and adjunctive therapy for decompression illness. Cochrane Database of Systematic Reviews 2007 , Issue 2 . Art. No.: CD005277. DOI: 10.1002/14651858.CD005277.pub2 .

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Dates

Assessed as Up-to-date: 5 November 2009
Date of Search: 23 October 2009
Next Stage Expected: 1 November 2012
Protocol First Published: Issue 2 , 2005
Review First Published: Issue 2 , 2007
Last Citation Issue: Issue 2 , 2007

What's new

Date	Event	Description
5 November 2009	Updated	We updated the search to October 23rd 2009. No new studies were found. We moved one ongoing study (Francis 2002) to the excluded studies section because the study did not continue and no data was supplied. We have removed one ongoing study from the review as it did not take place (Hink 2005).

History

Date	Event	Description
11 March 2008	Amended	Converted to new review format.

Abstract

Background

Decompression illness (DCI) is due to bubble formation in the blood or tissues following the breathing of compressed gas. Clinically, DCI may range from a trivial illness to loss of consciousness, death or paralysis. Recompression is the universally accepted standard for the treatment of DCI. When recompression is delayed, a number of strategies have been suggested in order to improve the outcome.

Objectives

To examine the effectiveness and safety of both recompression and adjunctive therapies in the treatment of DCI.

Search strategy

We searched CENTRAL (*The Cochrane Library* 2009, Issue 3); MEDLINE (1966 to October 2009); CINAHL (1982 to October 2009); EMBASE (1980 to October 2009); the Database of Randomised Controlled Trials in Hyperbaric Medicine (October 2009), and hand-searched journals and texts.

Selection criteria

We included randomized controlled trials that compared the effect of any recompression schedule or adjunctive therapy with a standard recompression schedule. We applied no language restrictions.

Data collection and analysis

Three authors extracted the data independently. We assessed each trial for internal validity and resolved differences by discussion. Data was entered into RevMan 4.2.

Main results

Two randomized controlled trials satisfied the inclusion criteria. Pooling of data was not possible. In one study there was no evidence of improved effectiveness with the addition of a non-steroidal anti-inflammatory drug (tenoxicam) to routine recompression therapy (at six weeks: relative risk (RR) 1.04, 95% confidence interval (CI) 0.90 to 1.20, P = 0.58) but there was a reduction in the number of compressions required when tenoxicam was added (P = 0.01, 95% CI 0 to 1). In the other study, the odds of multiple recompressions was lower with a helium and oxygen (heliox) table compared to an oxygen treatment table (RR 0.56, 95% CI 0.31 to 1.00, P = 0.05).

Authors' conclusions

Recompression therapy is standard for the treatment of DCI, but there is no randomized controlled trial evidence. Both the addition of an NSAID or the use of heliox may reduce the number of recompressions required, but neither improves the odds of recovery. The application of either of these strategies may be justified. The modest number of patients studied demands a cautious interpretation. Benefits may be largely economic and an economic analysis should be undertaken. There is a case for large randomized trials of high methodological rigour in order to define any benefit from the use of different breathing gases and pressure profiles during recompression therapy.

Plain language summary

Recompression therapy and adjunctive drug therapy for decompression illness (the bends)

Decompression illness (DCI) is due to the presence of bubbles in the tissues or blood vessels following the reduction of surrounding pressure (decompression). It is most commonly associated with breathing compressed gas while diving underwater. The effects of DCI may vary from the trivial to life-threatening and treatment is usually administered urgently. Recompression is applied while breathing 100% oxygen, based on the reduction in bubble size with pressure and more rapid elimination of nitrogen from the bubbles when breathing 100% oxygen. Recovery without recompression can be slow and incomplete and DCI is responsible for significant health problems in areas where recompression is unavailable. Recompression with 100% oxygen has become universally accepted as the appropriate therapy despite the lack of high quality clinical evidence of effectiveness. This review found only two randomized trials. One trial compared standard oxygen recompression to helium and oxygen recompression, while the other compared oxygen recompression alone to recompression and an adjunctive non-steroidal anti-inflammatory drug (NSAID). Both trials suggested these additional interventions may shorten the course of recompression required. For example, the use of an NSAID reduced the median number of recompression sessions required from three to two. We conclude there is little evidence for using one recompression strategy over another in the treatment of decompression illness and that the addition of an anti-inflammatory may shorten the course of recompression required. More research is needed.

Background

Decompression illness (DCI) is the term given to the clinical manifestations of bubble formation in the blood or tissues following a reduction in ambient pressure (Brubakk 1999). Decompression illness most commonly occurs in relation to compressed air or mixed gas diving, but it may also arise in aviators following rapid ascent to altitude or cabin decompression and in astronauts participating in 'space walks' (Moon 2003). The term covers two different problems: arterial gas embolism (AGE) caused by the presence of bubbles in the arterial blood vessels; and decompression sickness (DCS) caused by bubbles in the veins and tissues. Arterial gas embolism may arise with entry of bubbles into the pulmonary veins through damage to lung tissue from air trapped in the distal airways during ascent (pulmonary barotrauma); or via an abnormal communication between the right and left sides of the heart, where blood can pass from the venous circulation to the arterial circulation without going through the lungs. Direct venous to arterial passage of bubbles in this way avoids the lung capillaries, which act as a very effective filter for bubbles and allow the safe evolution of gas into the expired breath. Decompression sickness may develop when venous and tissue bubbles form from dissolved inert gas that accumulated during the period of time under pressure. Bubbles may cause harm through mechanical distortion of tissues, vascular obstruction or stimulation of immune mechanisms that lead to tissue oedema, haemoconcentration and hypoxia.

Arterial blood vessels are a particular target for damage by intravascular bubbles, where they disrupt the luminal surfactant layers, damage the endothelium and stimulate intraluminal blood elements (particularly white blood cells and platelets) to clump together and obstruct the flow within the vessel. Secondary interactions between these elements result in leaking vessels and further reductions to flow (Helps 1991; Hills 1991; Nossum 1999). This mechanism does not seem to be important with regard to venous bubbles, possibly due to the low pressure nature of this system.

The two pathological entities (AGE and DCS) are difficult to distinguish clinically and are treated with similar strategies (Francis 1988; Smith 1992). It is therefore, accepted practice to make the clinical diagnosis of 'DCI' in the understanding that one or both of the two pathologies may be operating. We will use the generic term DCI in this review except when we refer to the specific pathological mechanisms that cause AGE and DCS.

Clinically, DCI has many possible manifestations: from mild, vague constitutional symptoms to sudden loss of consciousness, death or paralysis (Francis 2003). The most important target tissues are the central nervous system and the musculoskeletal system, with musculoskeletal pain being the most common symptom in the early series. More recently it has been suggested that constitutional symptoms similar to those experienced during viral illness may be a manifestation of DCI (Francis 2003; Rudge 1991). Without an objective method of determining whether symptoms are due to bubble formation these mild symptoms will sometimes result in misdiagnosis. Severe illness is now uncommon in the developed world, but severe DCI leading to permanent disability or death remains a significant problem for poorly trained indigenous commercial divers around the developing world (Francis 2003; Moon 2003). While the overall incidence of DCI in that setting has not been determined, a number of studies have reported both incidence and prevalence of DCI and its long-term effects in individual diving populations. In one prospective study the proportion of divers who reported ever having DCI was 94.4%, and 10% had residual signs of spinal injury. Mortality was estimated at four percent of indigenous divers per year in another group (Bourke 1998; Cross 1998). In contrast, the incidence of DCI among recreational divers in Canada was estimated at 0.01% of dives over 14 months (Ladd 2002).

The historical development of recompression treatment tables was well described by Moon and Gorman (Moon 2003). Pol and Wattelle first proposed recompression (while breathing air) as a treatment for DCI in 1854 by Pol and Wattelle, but it was not used systematically in practice until 1896 during the construction of the Hudson river tunnel. This project involved many workers spending long shifts in a pressurized working chamber known as a caisson (Moir 1896). Mortality of 25% of cases recorded prior to institution of recompression was dramatically reduced with recompression. In a subsequent tunnel project in New York, Keays demonstrated a recurrence rate of symptoms of 13.7% in workers with DCI who were treated with analgesics and 'stimulants' compared to 0.5% when treated with recompression (Keays 1909). Recompression on air became the standard therapy for DCI until the introduction of 100% oxygen breathing during recompression in 1944, following the work of Yarbrough and Behnke (Yarbrough 1939).

Many variations of recompression on oxygen, air and helium and oxygen mixtures have been proposed and used since; however, recompression in some form remains the mainstay of treatment for DCI. A review of the effectiveness of the United States Navy oxygen treatment tables suggests complete relief of symptoms in 50% to 98% of individuals, apparently depending on the severity of illness and period of time elapsed between development of DCI and recompression (Thalmann 1996). In addition, a number of 'first aid' and adjunctive therapies have been applied in the hope of improving rates of complete resolution. Strategies suggested include the maintenance of a horizontal position (to prevent movement of intravascular bubbles into the cerebral circulation); 100% oxygen administration at one atmosphere; the administration of intravenous or oral fluids, corticosteroids, anticoagulants, non-steroidal anti-inflammatory drugs, lignocaine and diazepam. These strategies (and others) have been recently summarized by Moon (Moon 2003). It is important to consider that any one of these strategies might modify the outcome of DCS and AGE in opposite directions.

Recompression usually 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 greatly enhance the movement of nitrogen out of any bubbles down a steep diffusion gradient as well as to deliver a greatly increased partial pressure of oxygen to the tissues. At the same time, the volume of those bubbles is directly reduced through the operation of Boyle's Law (volume of a given mass of gas is inversely proportional to the ambient pressure). Typically, treatments involve pressurization to between two and six atmospheres absolute (ATA), for periods between two hours and several days. The optimal treatment strategy for differing clinical presentations is not apparent however by far the most commonly used regimen is the United States Navy Treatment Table 6 (USN TT6) - a 2.8ATA maximum pressure, 100% oxygen breathing schedule which lasts a total of four hours and 45 minutes (DAN 2001).

Objectives

The objective of this review was to examine the effectiveness and safety of both recompression and adjunctive therapies in the treatment of decompression illness. We assessed effectiveness by using a number of clinically important outcomes, including mortality, residual functional disability and severity scoring systems.

Methods

Criteria for considering studies for this review

Types of studies

We included all randomized and quasi-randomized controlled trials that examined the effectiveness and safety of therapy for DCI.

Types of participants

We included patients of any age or sex with DCI. We defined decompression illness as any symptom or sign, or both, arising after compressed gas breathing (including brief exposures such as during submarine escape training) and assessed clinically as likely to represent bubble injury. We excluded participants suffering from other causes of AGE (for example iatrogenic).

Types of interventions

We included trials comparing interventions that included recompression or an adjunctive therapy listed in this section, compared with another form of recompression or other therapy. Adjunctive therapies of interest were the administration of intravenous and oral fluids, or both; corticosteroids, anticoagulants, non-steroidal anti-inflammatory drugs, local anaesthetic agents such as lignocaine or benzodiazepines such as diazepam.

The comparator group was most likely to include recompression in some form. We accepted any treatment regimen designed to promote recovery after an episode of DCI including intensive combined therapies. Where regimens differed significantly between studies this was clearly stated and the implications discussed.

Types of outcome measures

We considered studies as eligible for inclusion if they reported any of the following outcome measures.

Primary outcomes

1. Mortality rate.
2. Severe functional disability rate or death. We took care to ensure death was included as a bad outcome when extracting data.
3. Complete recovery rate.

Secondary outcomes

1. Functional recovery scale (e.g. Royal New Zealand Navy (RNZN) Recovery Score (Mitchell 1998), Dick and Massey Score (Dick 1985), functional outcome scale (Bennett 1995)).
2. Number of recompression sessions required (in studies looking at adjunctive therapies only).
3. Time to complete recovery.
4. Time to return to diving.
5. Activities of daily living (ADL), (e.g. the Barthel Index).
6. Quality of life.
7. Adverse events following therapy (e.g. for recompression: barotrauma (aural, sinus, pulmonary in the short and long-term) and oxygen toxicity (short-term)). Any other recorded adverse effects were reported and discussed.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), (*The Cochrane Library* 2009, Issue 3); OVID MEDLINE (1966 to October 2009); OLDMEDLINE (1951 to 1965); EMBASE (1980 to October 2009); CINAHL (1982 to October 2009) and an additional database developed in our hyperbaric facility (the Database of Randomised Trials in Hyperbaric Medicine, Bennett 2004). The search strategy in Appendix 1 was used for MEDLINE and adapted for the other databases. We did not apply language restrictions.

Searching other resources

We also handsearched the following relevant publications:

- Hyperbaric textbooks (Brubakk 2003; Jain 1999; Kindwall 1999; Oriani 1996)
- Journals (*Undersea and Hyperbaric Medicine* 1992 to 2005; *Hyperbaric Medicine Review* 1986 to 1992; *South Pacific Underwater Medicine Society (SPUMS) Journal* 1973 to 2005; *European Journal of Hyperbaric Medicine* 1998 to 2005, and *Aviation, Space and Environmental Medicine Journal* 1980 to 2005)
- Conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society, International Congress of Hyperbaric Medicine) published from 1980 to October 2009.

We checked the reference lists of the trials and reviews. We also contacted current researchers in the field for information on unpublished data and ongoing trials.

Data collection and analysis

Trial identification

Records retrieved by the initial search were scanned by MB, JL and JW to exclude obviously irrelevant studies, two authors (MB and JW) then identified trials that may have met the inclusion criteria. Full-text articles were retrieved and reviewed by three authors (MB, JL and SM) for the purpose of applying inclusion criteria

independently. In all instances we resolved differences of opinion by discussion.

Data extraction

We contacted the authors of primary studies to provide information when missing or incomplete data were encountered. Two of us (MB and JW) assessed extracted data from each trial and entered it into RevMan 5.0. We resolved disagreement by discussion.

Quality assessment

We followed the guidelines set out by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). We assessed factors related to applicability of findings, validity of individual studies, and study design characteristics such as double blinding and adherence. We checked for sources of bias: selection, performance, attrition, and detection bias. Two authors independently assessed the methodological quality of the selected studies. They ranked allocation concealment as either A (adequate), B (unclear), C (inadequate) or D (not used). We resolved any differences of opinion by discussion and consensus.

Analyses

Pooling of data was not appropriate for this review. For proportions (dichotomous outcomes), we calculated relative risk (RR) with 95% confidence intervals (CI). All analyses were made on an intention-to-treat basis, where possible; where not possible, this is clearly stated. Where the 95% CI for the absolute risk difference did not cross zero, we calculated the number needed to treat (NNT) from the standard recompression event rate and the experimental group rate. The 95% CI was calculated from the 95% CI of the risk difference between the groups.

We performed sensitivity analyses for missing data from the outcome 'complete recovery' in Bennett 2003 by comparing best and worst case scenarios at discharge and six weeks. For the best case scenario, all missing patients in the tenoxicam group were assumed to have recovered while all those in the placebo group were assumed not to have recovered. The worst case scenario employed the reverse assumptions. We had also planned a sensitivity analysis by study quality however this was not appropriate. If appropriate data existed, we had also planned to consider subgroup analysis based on:

1. subtype of DCI (DCS (Type I, Type II), AGE;
2. severity grade;
3. gas burden;
4. time elapsed between completion of last dive and treatment. We intended to arbitrarily divide participants in to those being compressed within one hour, one to 12 hours and more than 12 hours since time of last dive;
5. time elapsed from appearance of first symptom to treatment (as above for categories);
6. dose of oxygen received (pressure less than 3.0 ATA versus 3.0 ATA or more and length of treatment course one session versus multiple sessions);
7. recompression with oxygen versus helium and oxygen mixtures.

Results

Description of studies

We identified 14 publications apparently dealing with the use of recompression or adjunctive therapy for the treatment of DCI. Initial examination confirmed six were investigations concerning divers, but for problems other than DCI (Davis 1987; Koltyn 1997; Saino 1992; Taylor 2000; Taylor 2001; Thorsen 1995); two were reviews without new data (Mitchell 2001; Moon 1997); one was a treatment guideline (Moon 1999); one was a comparative trial with retrospective controls (Shupak 1997); one was a trial involving pre-treatment with a range of adjunctive agents intended to modify any subsequent illness (Philp 1979); and one was a report of a planned trial (Francis 2002). These reports were excluded (see 'Characteristics of excluded studies' table) leaving two publications of possible randomized comparative trials. After appraisal of the full reports we included both these trials (Bennett 2003; Drewry 1994). Details are given in the 'Characteristics of included studies' table.

The authors are aware of two planned randomized controlled trials but believe that both have been abandoned at the time of writing (personal communication from the individuals who proposed the trials). One proposed the investigation of helium-oxygen mixtures versus oxygen only recompression (J. Hink - personal communication), while the other proposed investigating the addition of intravenous lignocaine to recompression for serious neurological DCI (Francis 2002).

In Bennett 2003, 180 participants presenting for management of DCI, but with exclusion of those with a clinical diagnosis of AGE, were randomized to either routine recompression therapy or routine recompression therapy with the addition of a non-steroidal anti-inflammatory drug (tenoxicam). Those with a firm clinical diagnosis of AGE were excluded on the basis of a lack of expectation of therapeutic benefit and some criticism that the administration of oral medication was not appropriate in this group (personal knowledge). The randomization schedule stratified those enrolled into five groups by disease severity, using a clinical scoring system. The recompression schedule was not specified in the protocol but prescribed at the discretion of the treating physician. In the active therapy arm, tenoxicam 20mg was administered at the first air break during recompression and daily for seven days, while in the control arm a placebo medication was administered on the same schedule. Results were given for 164 of the 180 enrolled (91%). The primary outcome variable in this trial was complete recovery of symptoms and signs measured at completion of recompression therapy and at six

weeks. Any mortality was also reported, as was the number of recompression sessions administered.

In Drewry 1994, 88 patients with a clinical diagnosis of DCI were randomized to an initial recompression schedule of either 100% oxygen breathing at 2.8 ATA (equivalent to 18 metres of seawater) pressure, with subsequent higher pressure options on oxygen and nitrogen mixtures if response was less than an 80% improvement, or a schedule involving breathing 50% oxygen with 50% helium at 2.8 ATA with similar higher pressure options breathing oxygen/helium mixtures in the event of less than 80% improvement. No details were given as to how an 80% improvement was calculated. This trial has been reported as interim results in an abstract only to date. Eighteen of the 88 participants (20.5%) were withdrawn from analysis due to failure to meet entry criteria (retrospectively) or because of protocol violations, and a further 14 had not reached final follow up. Therefore only 56 participants (64% of those enrolled) had outcomes reported in the abstract. This trial reported the proportion of participants who required multiple compressions prior to discharge.

Risk of bias in included studies

Randomization

Allocation concealment was adequate for Bennett 2003 (central allocation by pharmacy staff) but unclear for Drewry 1994. In the latter trial, it was not clear that the operational staff could not manipulate the group assignment by examination of the allocation envelope prior to recompression. Randomization procedures were described in both studies, being a computer-generated number sequence for Bennett 2003 and numbered envelopes for Drewry 1994 (personal communication).

Patient baseline characteristics

All participants had a clinical diagnosis of DCI. Bennett 2003 specifically excluded those with a clinical diagnosis of CAGE, while Drewry 1994 did not specify any exclusions. Drewry 1994 stratified the randomization for those presenting up to, or later than, 48 hours after the onset of symptoms. Bennett 2003 reported the number of participants with severity scores from 1 to 5 in each intervention group (see Table 1).

Blinding

Bennett 2003 described good blinding with the use of a placebo medication manufactured by the drug company that was presented in numbered containers. Only the pharmacist who performed the randomization coding held the key. Participants and attending medical officers were blinded in Drewry 1994; however, it may have been possible to discover allocation because of different voice timbre changes when breathing the different compressed gases in the two groups.

Participants lost to follow-up

Bennett 2003 lost a total of 16 of 180 participants (9%) at final follow-up, while Drewry 1994 did not report on 32 of the original 88 enrolled (36%). It was not clear to which arm these participants had been allocated.

Intention-to-treat analysis

Bennett 2003 specifically stated the use of an intention to treat while Drewry 1994 reported multiple violations of protocol and could not have used analysed by intention to treat.

Effects of interventions

Data from the two included studies could not be pooled and are described individually.

Bennett 2003 reported no difference in the proportion of participants who were completely recovered at discharge or six weeks later (at discharge: 59/84 (70%) in the placebo group versus 53/84 (63%) in the tenoxicam group, at six weeks: 64/80 (80%) with placebo versus 70/84 (83%) with tenoxicam). Analysis of the chance of recovery with tenoxicam as part of this review confirmed the lack of a significant effect (at discharge: relative risk (RR) for recovery with tenoxicam 0.90, 95% confidence interval (CI) 0.72 to 1.11, P = 0.33 (comparison 01, outcome 01); at six weeks RR for recovery with tenoxicam 1.04, 95% CI 0.90 to 1.20, P = 0.58, comparison 01, outcome 04). However, this result was sensitive to the outcome of those lost to follow up, with a best case analysis suggesting that the chance of recovering completely at six weeks was improved with tenoxicam (RR) 1.19, 95% CI 1.01 to 1.39, P = 0.03, comparison 03, outcome 05).

This trial reported a difference in the number of recompressions required to reach these outcomes. The placebo group required a median of three treatments (range one to eight), while the tenoxicam group required a median of two treatments (range one to six), this difference was reported as significant (P = 0.01, 95% CI 0 to 1). Analysis of the proportion of participants requiring more than two recompressions suggested a benefit from the administration of tenoxicam (55/90 (61%) of the placebo group versus 35/90 (39%) of the tenoxicam group). The RR for requiring more than two treatments with tenoxicam was 0.65 (95% CI 0.48 to 0.88, P = 0.005, comparison 01, outcome 07). A stratified analysis by the severity grade of DCI on presentation suggested this treatment effect was present across the range of severities tested. This analysis suggested a need to treat five patients to reduce the number of compressions required for one extra patient (NNT 5, 95% CI 3 to 18).

Drewry 1994 reported that the proportion of participants requiring multiple recompressions was significantly smaller in the oxygen and helium group (heliox) (9/25 (36%) versus 20/31 (65%), P = 0.03). Analysis in this review suggests the chance of multiple recompressions may be lower with heliox (RR 0..56, 95% CI 0.31 to 1.00, P = 0.05, comparison 02, outcome 01). This analysis suggests the need to treat four individuals with helium and

oxygen in order to have one extra individual requiring only a single recompression (NNT = 4, 95%CI 2 to 31).

Adverse events were reported by Bennett 2003. Six participants had problems during initial recompression, three (one on tenoxicam, two on placebo) complained of aural barotrauma, two (one on tenoxicam, one on placebo) developed premonitory signs of cerebral oxygen toxicity and one tenoxicam patient complained of nausea not resolved by removal from oxygen breathing at depth (pressure).

Discussion

We did not find randomized controlled trial evidence to support or refute the effectiveness of recompression versus no recompression for the management of DCI. Recompression is a universally accepted therapy for DCI and for ethical reasons is most unlikely to be subject to randomized investigation against sham therapy in the future. The two trials considered in this review looked at alternative recompression strategies (Drewry 1994) and an NSAID drug as an adjunctive therapy to standard recompression (Bennett 2003) respectively. The results could not therefore be pooled for meta-analysis.

The two trials involved a modest total of 268 patients. The Drewry 1994 trial was never reported at completion and is probably underpowered to find a clinically significant difference between the two recompression strategies. While a preliminary 1992 report on trial methodology (referenced here as a duplicate of (Drewry 1994) suggests a sequential analysis strategy with a stopping rule including a demonstrated difference between the groups at one month (P = 0.05 or less), it is not clear this rule was invoked. We believe the trial was abandoned shortly after the Drewry 1994 report because of continuing protocol violations (personal communication). There is a significant difference in the reported number of participants enrolled in each arm of this study (25 versus 31) and although this may be due to chance we consider the potential for selection bias to be high. One further problem is that this trial reported only the proportion of participants who required multiple recompressions and there were no available data on the clinical health outcomes at any stage. Bennett 2003 was powered to detect a difference between groups in the proportion of participants with complete resolution (30% placebo versus 20% tenoxicam predicted). This trial suggests we can be reasonably confident that the addition of tenoxicam to recompression does not result in an improvement in the effectiveness of therapy.

The proportion of participants requiring more than one recompression was significantly reduced by the use of an aggressive helium and oxygen recompression regimen in which treatment depth and duration was determined by symptom response (Drewry 1994). The impact of the heliox regimen should be interpreted carefully in the context of local patient characteristics and the expected rate of multiple compressions. While calculation of the NNT with heliox using the control event rate in this study (65% required multiple compression) is four, this estimate is sensitive to the actual event rate in practice at other treatment facilities. For example, data from 591 cases of DCI reported by the Divers Alert Network in 2001 suggest the proportion receiving multiple compressions is 50% (DAN 2001). Using this as the control event rate and an RR of 0.56 as our best estimate of effect suggests an NNT of five. Also of potential importance is the consideration that the treatment protocol was quite complex for both arms of the study and ultimately allowed for the participants to enter a saturation treatment that may have lasted for several days. This mode of treatment is unlikely to be a realistic prospect for most treatment facilities and the clinical relevance of this finding is therefore unclear. More information is needed on the actual profiles used and the clinical outcome of participants in this trial. This is important because it is possible that any benefit for heliox treatment may have arisen from an interaction with, complex, long, high pressure recompression protocols that might be impractical in many hyperbaric units. The most commonly used initial recompression regimen lasted four hours and 45 minutes with the option to extend beyond that time if resolution was incomplete.

The proportion of participants requiring more than two recompressions before discharge was significantly reduced by the addition of the NSAID Tenoxicam to a standard recompression treatment in Bennett 2003. We chose the dichotomous outcome 'one or two treatments versus more than two treatments' for two reasons. First, this was a planned analysis in Bennett 2003 based on a median requirement of three treatments using standard care prior to commencing the trial (personal knowledge). Second, the standard practice in many Australasian institutions is to continue recompression treatments until resolution of symptoms plus one further recompression session, or until symptoms plateau for two consecutive recompression sessions. Thus, for many physicians, two recompression sessions is a minimal treatment course. Analysis suggested a modest treatment-sparing effect with an NNT of five patients to reduce the number of recompression treatments required by at least one. A subgroup analysis by severity score suggested this benefit may extend across all severity grades, but was underpowered to produce a definitive result. Similar considerations concerning the interpretation of NNT apply here as well as to Drewry 1994, particularly as world practice suggests that single recompression therapy remains common. Once again using the DAN data for comparison (DAN 2001) and the effect estimate from the study (RR 0.65), only 30% of patients received more than two compressions, suggesting an NNT with tenoxicam of 10 rather than five.

An informal economic analysis based on the results of Bennett 2003 and using cost data from a contemporaneous cost analysis in the main contributing hyperbaric facility involved (Gomez-Castillo 2005), suggests there may be modest cost savings associated with the administration of tenoxicam as an adjunctive measure for DCI. These data suggest a saving of $AUD 720 (one session of HBOT for DCI) for every five patients treated for DCI (95% CI every 3 to 18 patients) This cost saving ignores the cost of the course of tenoxicam. While costs vary with the source of supply, a typical cost for 30 tablets in Australia is approximately $AUD 13.00. The

savings above would be reduced by approximately $AUD 6.50 for each patient if they were issued with only sufficient supply for the seven-day course (MIMS 2006).

We had also planned to perform subgroup analyses with respect to DCS type, time delay between symptoms and recompression, and dose of oxygen received. However, the paucity of eligible trials did not permit this approach. One further problem with research in this area is diagnostic uncertainty. There are no reliable diagnostic tests or clinical criteria for DCI and it is likely that all clinical trials will be contaminated by an unknown number of 'cases' that do not in fact suffer from a bubble-related injury. In general, this will tend to minimize the apparent effectiveness of specific, targeted therapies while magnifying the effect of symptomatic therapies with broad, non-specific activity. For the clinician, the included studies here are pragmatic and likely to reflect the efficacy of interventions in the presence of this diagnostic uncertainty.

There are a few major adverse effects of recompression (pulmonary barotrauma, acute cerebral oxygen toxicity or death related to chamber fire) and short courses of non-steroidal drugs (renal failure or significant gastric bleeding), and while these are all rare enough not to be seen in the trials included in this review, they should be included in consideration of any benefit of these therapies. In practice it is likely that a beneficial effect strong enough to be clearly identified in clinical trials would overwhelm the consideration of such rare events. There are, however, a number of more minor complications that may occur commonly and Bennett 2003 reported six individuals with minor adverse effects. None of the six were withdrawn from therapy.

Authors' conclusions

Implications for practice

Recompression therapy is universally accepted as standard practice for the treatment of DCI. While there is considerable evidence for good outcomes following recompression, this practice is not based on any randomized controlled trial evidence. There is some evidence that the addition of an NSAID to breathing 100% oxygen during recompression reduces the number of recompression sessions required to treat DCI, but no evidence for an improvement in the rate of complete recovery. Similarly, there is some evidence that helium and oxygen breathing during recompression may reduce recompression requirements, though the methodological problems in the single trial examining the use of helium and oxygen breathing should be noted. The use of an NSAID is likely to be associated with a modest reduction in the cost of therapy. Thus, the application of either of these strategies may be justified. The small number of studies and the modest numbers of patients included in this review demand a cautious interpretation. Given the lack of evidence for improved outcomes, benefits may be largely economic and an economic analysis should be undertaken.

Implications for research

Given the natural history of severe DCI and the well-documented clinical response to recompression, it is unlikely that any comparison of recompression therapy against a sham alternative can be justified. There is, however, a strong case for large randomized trials of high methodological rigour in order to define the extent of benefit (if any) from the use of different breathing gases and pressure profiles during recompression therapy. Specifically, information is required on the subset of disease severity that may justify the use of complex and expensive treatment tables. The diagnosis and classification of DCI is particularly problematic with the milder forms of the disease. Formal economic analysis is required to quantify the cost benefit of treatment with NSAIDs and heliox. Any future trials would need to consider in particular, the following.

- Appropriate sample sizes with power to detect the expected differences generated by this review.
- Careful definition and selection of target patients.
- Appropriate treatment schedules (gas mixtures, pressure and time).
- Appropriate supportive therapy to which recompression would be an adjunct.
- Effective and explicit blinding of outcome assessors.
- Appropriate outcome measures including all those listed in this review.
- Careful elucidation of any adverse effects.
- The cost utility of the therapy.

Acknowledgements

We would like to thank John Carlisle, Nathan Pace, Peter Kranke, Richard Moon, Tom S Neuman, James Vorosmarti, Robyn Walker, Janet Wale, Kathie Godfrey and Marcus Müllner for their help and editorial advice during the preparation of this review. We are also very grateful to Jane Cracknell of the Cochrane Anaesthesia Review Group for orchestrating the process.

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Conceiving the review: Bennett
Co-ordinating the review: Bennett
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Screening search results: Bennett, Mitchell
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RevMan statistical data: Bennett
Other statistical analysis not using RevMan: Bennett
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Interpretation of data: Bennett, Mitchell, Lehm
Statistical inferences: Bennett
Writing the review: Bennett
Securing funding for the review: none received
Performing previous work that was the foundation of the present review: Bennett, Mitchell, Lehm
Guarantor for the review (one author): Bennett
Person responsible for reading and checking review before submission: Lehm, Wasiak

Declarations of interest

Three of the authors of this review are diving physicians (MB, JL, SM) and both MB and SM are authors of trials included in this review. There are no known financial conflicts of interest.

Differences between protocol and review

Published notes

Characteristics of studies

Characteristics of included studies

Bennett 2003

Methods	Randomized controlled trial with allocation concealment, blinding of all participants and investigators. Analysed by intention to treat. Central computer code held by pharmacy.
Participants	180 participants with clinical DCI (excluding CAGE) from three centres.
Interventions	Control: recompression on physician choice table (88% had USN TT6), placebo medication at first air break and daily for seven days, recompression as clinically indicated to plateau of symptoms or complete resolution plus one further treatment. Active: as above, but active medication with tenoxicam 20mg per dose.
Outcomes	Death, outcome functional score (see table 02), number of compression cycles required.
Notes	

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Yes	A - Adequate

Drewry 1994

Methods	Randomized controlled trial with blinding of investigators and participants. Sealed envelope method with stratification for presentation within 48 hours or more than 48 hours.
Participants	88 patients presenting with DCI (clinical diagnosis) and requiring recompression therapy.
Interventions	Control: intravenous hydration and recompression breathing 100% oxygen at 18msw. If 80% or more improvement after 45 minutes, then USN TT6 recompression table is completed. If less than 80% improvement, then proceeded to 30msw breathing 50% oxygen with 50% nitrogen. Complex algorithm if there is still poor response, with maximum compression to 50msw. Active: intravenous hydration and recompression breathing 50% oxygen and 50% helium at 18msw. If 80% or more improvement after 45 minutes, then completed an 18msw maximum depth table breathing heliox with no air breaks. If less than 80% improvement, then proceeded to 30msw breathing 50% oxygen with 50% helium. Complex algorithm if there is still poor response, with maximum compression to 50msw breathing 20% oxygen and 80% helium.
Outcomes	Proportion of participants requiring second recompression due to incomplete resolution of clinical symptoms or signs.
Notes	Full trial only reported in abstract. Not analysed by intention to treat (18 withdrawals due to protocol violations and 14 others with results not reported). The first report did not give any results.

Risk of bias table

Item	Judgement	Description
Allocation concealment?	Unclear	B – Unclear

Footnotes

DCI = Decompression illness
CAGE = Cerebral arterial gas embolus
HBOT =Hyperbaric oxygen therapy
USN TT6 = United States Navy treatment table six = an 18m maximum pressure table breathing 100% oxygen
msw Metres of seawater = (a measure of treatment pressure, 10msw = 1 atmosphere)

Characteristics of excluded studies

Davis 1987

Reason for exclusion	Not investigating the treatment of DCI

Francis 2002

Reason for exclusion	Trial was abandoned before recruitment commenced.

Koltyn 1997

Reason for exclusion	Not investigating the treatment of DCI

Mitchell 2001

Reason for exclusion	Review only: no new data

Moon 1997

Reason for exclusion	Review only: no new data

Moon 1999

Reason for exclusion	Guidelines for therapy: no new data

Philp 1979

Reason for exclusion	Pre-treatment (before diving) study for the prevention and amelioration of DCI

Saino 1992

Reason for exclusion	Not investigating the treatment of DCI

Shupak 1997

Reason for exclusion	Comparative trial with retrospective controls

Taylor 2000

Reason for exclusion	Not investigating the treatment of DCI

Taylor 2001

Reason for exclusion	Not investigating the treatment of DCI

Thorsen 1995

Reason for exclusion	Not investigating the treatment of DCI

Footnotes

DCI = Decompression illness
RCT = Randomized controlled trial

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

1 Outcome scores used by Bennett 2003

Outcome score
1. Well, no symptoms or signs
2. Minor symptoms or signs not effecting daily life (examples: intermittent tingling in an extremity or minor discomfort not requiring analgesia)
3. Moderate symptoms or signs resulting in some effect on daily life (examples: continued pain requiring analgesia, weakness, hypoasthesia)
4. Major symptoms or signs significantly effecting life (examples: paraparesis, cognitive dysfunction requiring employment change)
5. Dead

Footnotes

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Ongoing studies

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Classification pending references

Data and analyses

1 Recompression with tenoxicam versus without tenoxicam

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Completely recovery at discharge	1		Risk Ratio (M-H , Fixed , 95% CI)	No totals
1.2 Complete recovery at discharge (best case scenario)	1		Risk Ratio (M-H , Fixed , 95% CI)	No totals
1.3 Complete recovery at discharge (worst case scenario)	1		Risk Ratio (M-H , Fixed , 95% CI)	No totals

1.4 Complete recovery at six weeks	1		Risk Ratio (M-H , Fixed , 95% CI)	No totals
1.5 Complete recovery at six weeks (best case scenario)	1		Risk Ratio (M-H , Fixed , 95% CI)	No totals
1.6 Complete recovery at six weeks (worst case scenario)	1		Risk Ratio (M-H , Fixed , 95% CI)	No totals
1.7 More than two recompressions administered	1	180	Risk Ratio (M-H , Fixed , 95% CI)	0.65 [0.48, 0.88]
1.7.1 DCI grade 1 (pain only) on admission	1	34	Risk Ratio (M-H , Fixed , 95% CI)	0.39 [0.15, 1.06]
1.7.2 DCI grade 2 on admission (mild neurological symptoms)	1	113	Risk Ratio (M-H , Fixed , 95% CI)	0.75 [0.52, 1.07]
1.7.3 DCI grade 3, 4 or 5 on admission (neurological signs, nausea or vertigo)	1	33	Risk Ratio (M-H , Fixed , 95% CI)	0.55 [0.28, 1.10]

2 Recompression using heliox or oxygen tables

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Multiple recompressions required	1		Risk Ratio (M-H , Fixed , 95% CI)	No totals

Figures

Sources of support

Internal sources

- No internal support, Not specified

External sources

- No external support, Not specified

Feedback

Appendices

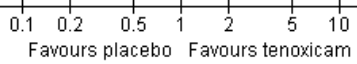
1 Sample search strategy (MEDLINE OVID)

1. Decompression sickness/
2. Embolism, Air/
3. Diving/
4. Decompression/
5. or/1-4
6. Recompression.tw
7. Hyperbaric Oxygenation/
8. Oxygen Inhalation Therapy/
9. Oxygen/ae, tu [Adverse Effects, Therapeutic Use]
10. atmospheric pressure/
11. Atmosphere Exposure Chambers/
12. (hyperbar$ or HBO$).tw.
13. (high pressure oxygen or 100% oxygen).tw.
14. ((monoplace or multiplace) adj5 chamber$).tw.
15. or/6-14
16. Anti-inflammatory Agents/
17. Adrenal Cortex Hormones/
18. Lidocaine/
19. Infusions, Intravenous/
20. Benzodiazepines/
21. or/16-20
22. 5 and 15
23. 5 and 21
24. 22 or 23
25. limit 24 to human

Graphs

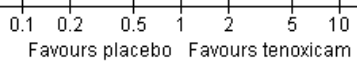
Comparison: 1 Recompression with tenoxicam versus without tenoxicam
Outcome: 1 Completely recovery at discharge

Study or sub-category	Tenoxicam n/N	Placebo n/N	RR MH, Fixed, 95% CI	Weight %	RR MH, Fixed, 95% CI
Bennett 2003	53 / 84	59 / 84		0.0	0.90 [0.72, 1.11]



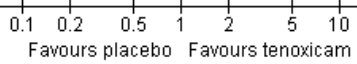
Comparison: 1 Recompression with tenoxicam versus without tenoxicam
Outcome: 2 Complete recovery at discharge (best case scenario)

Study or sub-category	Tenoxicam n/N	Placebo n/N	RR MH, Fixed, 95% CI	Weight %	RR MH, Fixed, 95% CI
Bennett 2003	59 / 90	59 / 90		0.0	1.00 [0.81, 1.24]



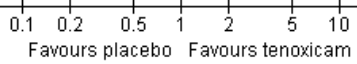
Comparison: 1 Recompression with tenoxicam versus without tenoxicam
Outcome: 3 Complete recovery at discharge (worst case scenario)

Study or sub-category	Tenoxicam n/N	Placebo n/N	RR MH, Fixed, 95% CI	Weight %	RR MH, Fixed, 95% CI
Bennett 2003	53 / 90	65 / 90		0.0	0.82 [0.66, 1.01]



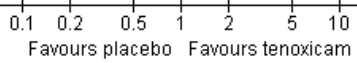
Comparison: 1 Recompression with tenoxicam versus without tenoxicam
Outcome: 4 Complete recovery at six weeks

Study or sub-category	Tenoxicam n/N	Placebo n/N	RR MH, Fixed, 95% CI	Weight %	RR MH, Fixed, 95% CI
Bennett 2003	70 / 84	64 / 80		0.0	1.04 [0.90, 1.20]



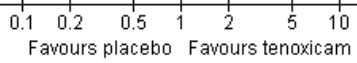
Comparison: 1 Recompression with tenoxicam versus without tenoxicam
Outcome: 5 Complete recovery at six weeks (best case scenario)

Study or sub-category	Tenoxicam n/N	Placebo n/N	RR MH, Fixed, 95% CI	Weight %	RR MH, Fixed, 95% CI
Bennett 2003	76 / 90	64 / 90		0.0	1.19 [1.01, 1.39]

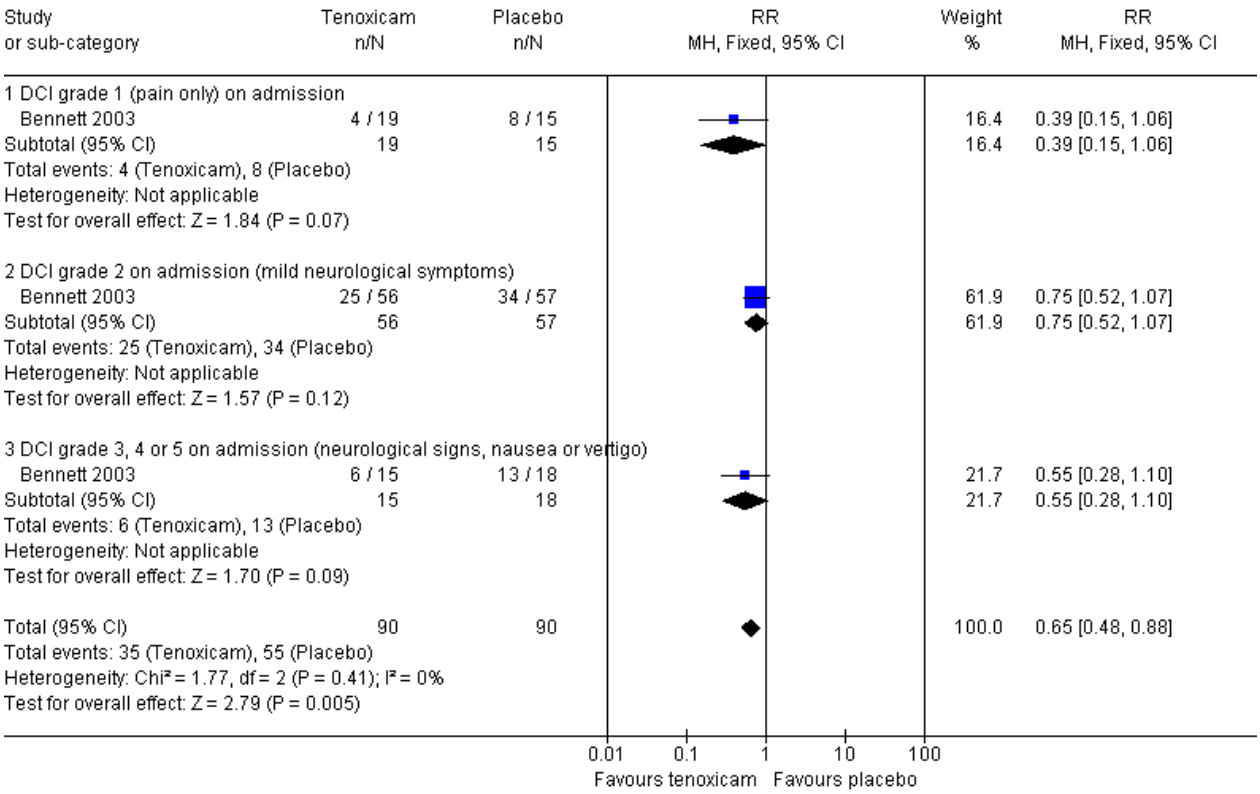


Comparison: 1 Recompression with tenoxicam versus without tenoxicam
Outcome: 6 Complete recovery at six weeks (worst case scenario)

Study or sub-category	Tenoxicam n/N	Placebo n/N	RR MH, Fixed, 95% CI	Weight %	RR MH, Fixed, 95% CI
Bennett 2003	70 / 90	74 / 90		0.0	0.95 [0.82, 1.10]



Comparison: 1 Recompression with tenoxicam versus without tenoxicam
Outcome: 7 More than two recompressions administered



Comparison: 2 Recompression using heliox or oxygen tables
Outcome: 1 Multiple recompressions required